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Concise International Chemical Assessment Document 38

N-NITROSODIMETHYLAMINE

First draft prepared by
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The **International Programme on Chemical Safety (IPCS)**, established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organization (ILO), and the World Health Organization (WHO). The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

The **Inter-Organization Programme for the Sound Management of Chemicals (IOMC)** was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, the United Nations Institute for Training and Research, and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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FOREWORD

Concise International Chemical Assessment Documents (CICADs) are the latest in a family of publications from the International Programme on Chemical Safety (IPCS) — a cooperative programme of the World Health Organization (WHO), the International Labour Organization (ILO), and the United Nations Environment Programme (UNEP). CICADs join the Environmental Health Criteria documents (EHCs) as authoritative documents on the risk assessment of chemicals.

International Chemical Safety Cards on the relevant chemical(s) are attached at the end of the CICAD, to provide the reader with concise information on the protection of human health and on emergency action. They are produced in a separate peer-reviewed procedure at IPCS. They may be complemented by information from IPCS Poison Information Monographs (PIM), similarly produced separately from the CICAD process.

CICADs are concise documents that provide summaries of the relevant scientific information concerning the potential effects of chemicals upon human health and/or the environment. They are based on selected national or regional evaluation documents or on existing EHCs. Before acceptance for publication as CICADs by IPCS, these documents undergo extensive peer review by internationally selected experts to ensure their completeness, accuracy in the way in which the original data are represented, and the validity of the conclusions drawn.

The primary objective of CICADs is characterization of hazard and dose–response from exposure to a chemical. CICADs are not a summary of all available data on a particular chemical; rather, they include only that information considered critical for characterization of the risk posed by the chemical. The critical studies are, however, presented in sufficient detail to support the conclusions drawn. For additional information, the reader should consult the identified source documents upon which the CICAD has been based.

Risks to human health and the environment will vary considerably depending upon the type and extent of exposure. Responsible authorities are strongly encouraged to characterize risk on the basis of locally measured or predicted exposure scenarios. To assist the reader, examples of exposure estimation and risk characterization are provided in CICADs, whenever possible. These examples cannot be considered as representing all possible exposure situations, but are provided as guidance only. The reader is referred to EHC 170[1] for advice on the derivation of health-based guidance values.

While every effort is made to ensure that CICADs represent the current status of knowledge, new information is being developed constantly. Unless otherwise stated, CICADs are based on a search of the scientific literature to the date shown in the executive summary. In the event that a reader becomes aware of new information that would change the conclusions drawn in a CICAD, the reader is requested to contact IPCS to inform it of the new information.

Procedures

The flow chart on page 2 shows the procedures followed to produce a CICAD. These procedures are designed to take advantage of the expertise that exists around the world — expertise that is required to produce the high-quality evaluations of toxicological, exposure, and other data that are necessary for assessing risks to human health and/or the environment. The IPCS Risk Assessment Steering Group advises the Co-ordinator, IPCS, on the selection of chemicals for an IPCS risk assessment, the appropriate form of the document (i.e., EHC or CICAD), and which institution bears the responsibility of the document production, as well as on the type and extent of the international peer review.

The first draft is based on an existing national, regional, or international review. Authors of the first draft are usually, but not necessarily, from the institution that developed the original review. A standard outline has been developed to encourage consistency in form. The first draft undergoes primary review by IPCS and one or more experienced authors of criteria documents to ensure that it meets the specified criteria for CICADs.

The draft is then sent to an international peer review by scientists known for their particular expertise and by scientists selected from an international roster compiled by IPCS through recommendations from IPCS national Contact Points and from IPCS Participating Institutions. Adequate time is allowed for the selected experts to undertake a thorough review. Authors are required to take reviewers' comments into account and revise their draft, if necessary. The resulting second draft is submitted to a Final Review Board together with the reviewers' comments.

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[1] International Programme on Chemical Safety (1994) *Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits.* Geneva, World Health Organization (Environmental Health Criteria 170).

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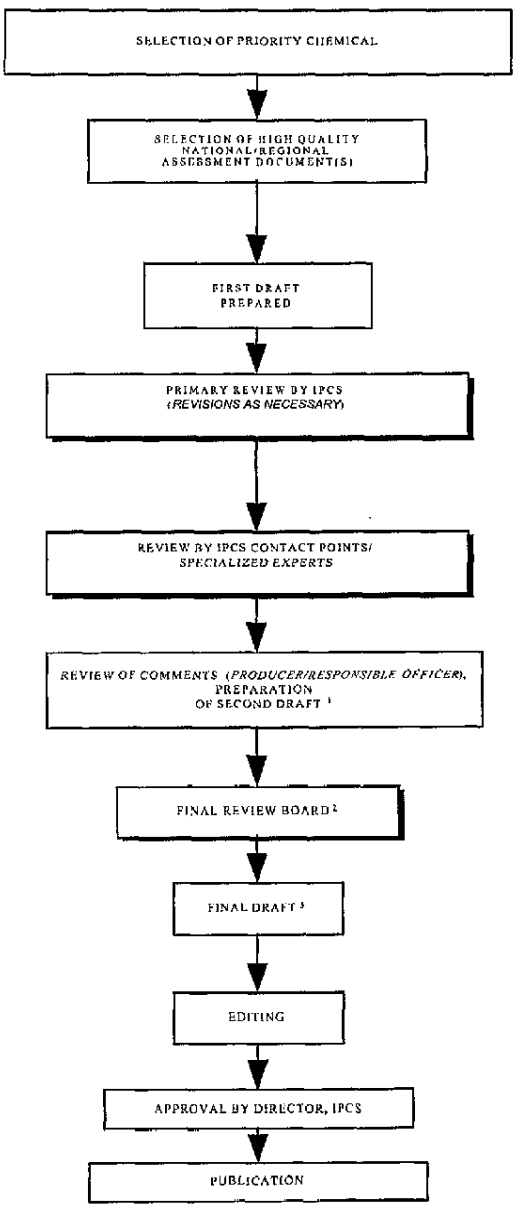
CICAD PREPARATION FLOW CHART



1 Taking into account the comments from reviewers.
2 The second draft of documents is submitted to the Final Review Board together with the reviewers' comments.
3 Includes any revisions requested by the Final Review Board.

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A consultative group may be necessary to advise on specific issues in the risk assessment document.

The CICAD Final Review Board has several important functions:

- to ensure that each CICAD has been subjected to an appropriate and thorough peer review;
- to verify that the peer reviewers' comments have been addressed appropriately;
- to provide guidance to those responsible for the preparation of CICADs on how to resolve any remaining issues if, in the opinion of the Board, the author has not adequately addressed all comments of the reviewers; and
- to approve CICADs as international assessments.

Board members serve in their personal capacity, not as representatives of any organization, government, or industry. They are selected because of their expertise in human and environmental toxicology or because of their experience in the regulation of chemicals. Boards are chosen according to the range of expertise required for a meeting and the need for balanced geographic representation.

Board members, authors, reviewers, consultants, and advisers who participate in the preparation of a CICAD are required to declare any real or potential conflict of interest in relation to the subjects under discussion at any stage of the process. Representatives of nongovernmental organizations may be invited to observe the proceedings of the Final Review Board. Observers may participate in Board discussions only at the invitation of the Chairperson, and they may not participate in the final decision-making process.

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1. EXECUTIVE SUMMARY

This CICAD on *N*-nitrosodimethylamine (NDMA) was prepared jointly by the Environmental Health Directorate of Health Canada and the Commercial Chemicals Evaluation Branch of Environment Canada based on documentation prepared concurrently as part of the Priority Substances Program under the *Canadian Environmental Protection Act* (CEPA). The objective of assessments on Priority Substances under CEPA is to assess potential effects of indirect exposure in the general environment on human health as well as environmental effects. Although occupational exposure was not addressed in the source document (Environment Canada & Health Canada, 2001), information on this aspect has been included in this CICAD. Data identified as of the end of August 1998 (environmental effects) and August 1999[1] (human health effects) were considered in this review. Other reviews that were also consulted include IARC (1978), ATSDR (1989), OME (1991, 1998), and BIBRA Toxicology International (1997, 1998). Information on the nature of the peer review and availability of the source document is presented in Appendix 1. Information on the peer review of this CICAD is presented in Appendix 2. This CICAD was approved as an international assessment at a meeting of the Final Review Board, held in Geneva, Switzerland, on 8–12 January 2001. Participants at the Final Review Board meeting are listed in Appendix 3. The International Chemical Safety Card for NDMA (ICSC 0525), produced by the International Programme on Chemical Safety (IPCS, 1993), has also been reproduced in this document.

N-Nitrosodimethylamine (NDMA) is the simplest dialkylnitrosamine. It is no longer used industrially or commercially in Canada or the USA but continues to be released as a by-product and contaminant from various industries and from municipal wastewater treatment plants. Major releases of NDMA have been from the manufacture of pesticides, rubber tires, alkylamines, and dyes. NDMA may also form under natural conditions in air, water, and soil as a result of chemical, photochemical, and biological processes and has been detected in drinking-water and in automobile exhaust.

Photolysis is the major pathway for the removal of NDMA from surface water, air, and land. However, in surface waters with high concentrations of organic substances and suspended matter, photodegradation is much slower. In subsurface water and in soil, biodegradation is the removal pathway of importance. NDMA is unlikely to be transported over long distances in air or to partition to soil and sediments. Because of its solubility and low partition coefficient, NDMA has the potential to leach into and persist in groundwater. It is metabolized and does not bioaccumulate. NDMA is generally not detectable in surface waters, except for localized contamination from industrial sites, where end-of-pipe effluent concentrations as high as 0.266 µg/litre have been measured.

In limited surveys in the country on which the sample risk characterization is based (i.e., Canada), NDMA has not been detected in ambient air, except in the vicinity of industrial sites. Low concentrations of NDMA — formed in water treatment plants or from groundwater contaminated by industrial effluents, for example — have been measured in drinking-water. The presence of NDMA has been demonstrated in some foods, most frequently in beer, cured meat, fish products, and some cheeses, although levels of NDMA have decreased in these products in recent years owing to changes in food processing. Exposure can also result from the use of consumer products that contain NDMA, such as cosmetics and personal care products, products containing rubber, and tobacco products.

Based upon laboratory studies in which tumours have been induced in all species examined at relatively low doses, NDMA is clearly carcinogenic. There is overwhelming evidence that NDMA is mutagenic and clastogenic. While the mechanism by which NDMA induces tumours is not fully elucidated, DNA adducts (in particular, O^6-methylguanine) formed by the methyldiazonium ion generated during metabolism likely play a critical role. Qualitatively, the metabolism of NDMA appears to be similar in humans and animals; as a result, it is considered highly likely that NDMA is carcinogenic to humans, potentially at relatively low levels of exposure.

Data on non-neoplastic effects in laboratory animals associated with exposure to NDMA are limited, attributable primarily to the focus on its carcinogenicity. Effects on the liver and kidney in repeated-dose toxicity studies, embryo toxicity and embryo lethality in single-dose developmental studies, and a range of immunological effects (suppression of humoral- and cell-mediated immunity) reversible at lowest concentrations have been reported.

[1] New information flagged by the reviewers and in a literature search conducted prior to the Final Review Board meeting has been scoped to indicate its likely impact on the essential conclusions of this assessment, primarily to establish priority for its consideration in an update. More recent information not critical to the hazard characterization or exposure–response analysis, considered by reviewers to add to informational content, has been added.

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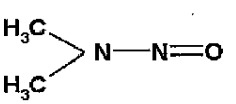
Cancer is clearly the critical end-point for quantitation of exposure–response for risk characterization of NDMA. In addition to it being best characterized, in general, tumours occur at lowest concentration, compared with those typically reported to induce non-cancer effects. The lowest tumorigenic $dose_{05}$ for the development of hepatic tumours in male and female rats exposed to NDMA in the critical study was 34 µg/kg body weight per day for the development of biliary cystadenomas in female animals. This equates to a unit risk of 1.5×10^{-3} per µg/kg body weight. Based on estimated intakes of NDMA in ambient air and contaminated drinking-water (groundwater) in the sample risk characterization, risks in the vicinity of industrial point sources are $>10^{-5}$. Those for ambient drinking-water are between 10^{-7} and 10^{-5}. NDMA is a genotoxic carcinogen, and exposure should be reduced to the extent possible.

Acute and chronic toxicity data are available for aquatic organisms. The toxic effect that occurred at lowest concentration was a reduction in the growth of algae at 4000 µg/litre. In the sample risk characterization, concentrations of NDMA in surface waters in the source country are less than the threshold for adverse effects estimated for aquatic organisms. Data on concentrations of NDMA in sediments or in soil in the sample country were not identified.

2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES

N-Nitrosodimethylamine, or NDMA, is the simplest dialkylnitrosamine, with a molecular formula of $C_2H_6N_2O$ and a relative molecular mass of 74.08 (ATSDR, 1989) (Figure 1). NDMA belongs to a class of chemicals known as *N*-nitroso compounds, characterized by the *N*-nitroso functional group (–N–N=O), and to the family of nitrosamines, which, in addition, possess an amine function ($–NR_2$, where R is H or an alkyl group). NDMA is also known as dimethylnitrosamine, dimethylnitrosoamine, *N*,*N*-dimethylnitrosamine, *N*-methyl-*N*-nitrosomethanamine, *N*-nitroso-*N*,*N*-dimethylamine, DMN, and DMNA. NDMA has the Chemical Abstracts



Service (CAS) registry number 62-75-9.

Figure 1: Chemical structure of NDMA.

NDMA is a volatile, combustible, yellow, oily liquid. It is susceptible to photolytic breakdown due to its absorption of ultraviolet light (Sax & Lewis, 1987). The physical/chemical properties relevant to the environmental fate of NDMA and utilized in the modelling of environmental partitioning (section 5.6) are presented in Table 1. Additional properties are presented in the International Chemical Safety Card reproduced in this document.

Table 1: Physical and chemical properties of NDMA.

Physical/chemical property	Value[a]
Melting point (°C)	50
Boiling point (°C)	151–154
Log K_{ow}	0.57
Vapour pressure	1080 Pa (25 °C)
Henry's law constant	3.34 Pa m³/mol (25 °C)
Solubility	miscible

[a] Includes experimental and calculated values listed in Callahan et al. (1979); Clayton & Clayton (1981); ATSDR (1989); Budavari et al. (1989); OME (1991); DMER & AEL (1996).

The conversion factor for NDMA in air is 1 ppm = 3.08 mg/m³.

3. ANALYTICAL METHODS

Analytical methods for NDMA consist of concentration followed by chromatographic separation of the components in the extract and detection of the *N*-nitrosamine. Concentration steps include liquid–liquid extraction and solid-phase extraction. Chromatographic separations have been achieved almost exclusively by gas chromatography. Detection of NDMA has been accomplished by flame ionization detectors (Nikaido et al., 1977), nitrogen–phosphorus detectors (US EPA, 1984), the Hall electrolytic conductivity detector operated in the reductive mode (von Rappard et al., 1976; US EPA, 1984), the thermal energy analyser or chemiluminescent nitrogen detector (Fine et al., 1975; Fine & Rounbehler, 1976; Webb et al., 1979; Kimoto et al., 1981; Parees & Prescott, 1981; Sen & Seaman, 1981a; Sen et al., 1994; Tomkins et al., 1995; Tomkins & Griest, 1996), and mass spectrometry. NDMA is also analysed by electron ionization low-resolution mass spectrometry (Sen et al., 1994), high-resolution mass spectrometry (Taguchi et al., 1994; Jenkins et al., 1995), chemical ionization tandem mass spectrometry on an ion trap mass spectrometer (Plomley et al., 1994), and laser

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ionization time-of-flight mass spectrometry (Opsal & Reilly, 1986). Liquid chromatography has also been used in conjunction with a photolysis reactor and (electrospray ionization) mass spectrometry (Volmer et al., 1996). Detection limits range from 0.150 µg/litre using nitrogen–phosphorus detectors (US EPA, 1984) to 0.002 µg/litre using a gas chromatograph–thermal energy analyser (Kimoto et al., 1981; Tomkins et al., 1995; Tomkins & Griest, 1996) to 0.001 µg/litre using gas chromatography–high-resolution mass spectrometry (Taguchi et al., 1994; Jenkins et al., 1995). Comparable detection limits are possible with chemical ionization tandem mass spectrometry on an ion trap mass spectrometer (Plomley et al., 1994).

4. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

Data on sources and emissions from the source country of the national assessment on which the CICAD is based (i.e., Canada) are presented here as an example. Sources and patterns of emissions in other countries are expected to be similar, although quantitative values may vary.

4.1 Natural sources

NDMA can be formed as a result of biological, chemical, or photochemical processes (Ayanaba & Alexander, 1974). It may be present in water, air, and soil due to chemical reaction between ubiquitous, naturally occurring precursors classified as nitrosatable substrates (secondary amines) or nitrosating agents (nitrites) (OME, 1998). For example, NDMA may form in air during nighttime as a result of the atmospheric reaction of dimethylamine (DMA) with nitrogen oxides (Cohen & Bachman, 1978). Soil bacteria may also synthesize NDMA from various precursor substances, such as nitrate, nitrite, and amine compounds (ATSDR, 1989). NDMA precursors are widespread throughout the environment, occurring in plants, fish, algae, urine, and faeces (Ayanaba & Alexander, 1974).

4.2 Anthropogenic sources

NDMA is produced as a by-product of industrial processes that use nitrate and/or nitrites and amines under a range of pH conditions. This is due to inadvertent formation when alkylamines, mainly DMA and trimethylamine, come into contact and react with nitrogen oxides, nitrous acid, or nitrite salts or when trans-nitrosation via nitro or nitroso compounds occurs (ATSDR, 1989). Therefore, NDMA may be present in discharges of such industries as rubber manufacturing, leather tanning, pesticide manufacturing, food processing, foundries, and dye manufacturing and, as a result, in sewage treatment plant effluent. Almost all of the releases in the source country (i.e., Canada) are to water.

NDMA has also been detected in emissions from diesel vehicle exhaust (Goff et al., 1980).

NDMA may form directly in sewage as a result of the biological and chemical transformation of alkylamines in the presence of nitrate or nitrite (Ayanaba & Alexander, 1974; ATSDR, 1989). It may also be released into the environment as the result of application of sewage sludge to soils rich in nitrate or nitrite.

NDMA may also be formed during the treatment of drinking-water (OME, 1994). NDMA's precursor, DMA, together with nitrite, may enter surface water streams from agricultural runoff (V.Y. Taguchi, personal communication, 1998). Water treatment plants incorporating a chlorination process (e.g., sodium hypochlorite) will produce NDMA from these precursors (Jobb et al., 1993; Graham et al., 1996). Ultraviolet treatment can decompose NDMA to DMA (Jobb et al., 1994). However, it is also possible to generate/regenerate NDMA from the DMA within distribution systems that have post-chlorination (V.Y. Taguchi, personal communication, 1998).

NDMA may be released into the environment as a result of use of certain pesticides contaminated with this compound (Pancholy, 1978). NDMA is present in various technical and commercial pesticides used in agriculture, hospitals, and homes as the result of its formation during the manufacturing process and during storage. The following DMA formulation pesticides may contain NDMA as a microcontaminant: bromacil, benazolin, 2,4-D, dicamba, MCPA, and mecoprop (J. Ballantine, personal communication, 1997; J. Smith, personal communication, 1999).

Since 1990, in testing in Canada of over 100 samples of formulated pesticidal products (DMA salt of phenoxy acid herbicides) potentially contaminated by NDMA, the compound was detected in 49% of the samples, with an average concentration of 0.44 µg/g. Only six samples contained concentrations above 1.0 µg/g, with a range from 1.02 to 2.32 µg/g. Concentrations in pesticides have decreased over time. In 1994, approximately 1 million kilograms of DMA-formulated phenoxy acid herbicides for commercial use were applied to the terrestrial environment in Canada (G. Moore, personal communication, 1999). Based on the average concen

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tration of NDMA mentioned above and per cent estimate of detection, it was calculated that approximately 200 g of NDMA may have been released into the environment through the use of these herbicides.

4.3 Production and use

There are no industrial or commercial uses of NDMA in Canada or the USA. NDMA was used in Canada in the past and may still be used in other countries in rubber formulations as a fire retardant and in the organic chemical industry as an intermediate, catalyst, antioxidant, additive for lubricants, and softener of copolymers (ATSDR, 1989; Budavari et al., 1989).

5. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

5.1 Air

NDMA has a low vapour pressure (1080 Pa at 25 °C), and, if emitted to or formed in air, it is not likely to adsorb to airborne particulate matter and is expected to exist almost entirely in the vapour phase. In daylight, it degrades rapidly by direct photolysis to form dimethylnitramine. The photolytic half-life of NDMA vapour exposed to sunlight ranges between 0.5 and 1.0 h (Hanst et al., 1977). Half-lives for the reaction with hydroxyl radicals range from 25.4 to 254 h in air (Atkinson, 1985). Modelling of environmental partitioning (section 5.6) is based on a half-life for NDMA in air of 5 h (DMER & AEL, 1996). The short half-lives for NDMA in air suggest that it is not persistent in this compartment.

5.2 Water

Since NDMA is miscible in water and has a low vapour pressure and a low octanol/water partition coefficient (log K_{ow} of • 0.57), it is not likely to bioaccumulate, adsorb to particulates, or volatilize to any significant extent (Thomas, 1982; ATSDR, 1989; OME, 1991). Oxidation, hydrolysis, biotransformation, and biodegradation are not significant factors affecting the fate of NDMA in lake water (Tate & Alexander, 1975). Photodegradation is the main process for removing NDMA from the aquatic environment. The efficiency of removal of NDMA depends on the characteristics of the particular water environment. Typically, photodegradation of NDMA is much slower in waters with high concentrations of organic substances and suspended solids than in clear water bodies. The rate of degradation through photolysis may be significantly decreased in the presence of interferences with light transmission, such as ice cover on receiving water bodies (Conestoga-Rovers & Associates, 1994; E. McBean, personal communication, 1999). This observation is supported in the groundwater compartment, where, in the absence of light, NDMA has the potential to persist (OME, 1991).

Modelling of environmental partitioning (section 5.6) is based on a mean half-life of 17 h for NDMA in surface water at 25 °C (DMER & AEL, 1996). Howard et al. (1991) reported a half-life range for NDMA in groundwater of 1008–8640 h, based on estimated unacclimated aqueous aerobic biodegradation.

5.3 Sediment

Modelling of environmental partitioning (section 5.6) is based on a mean half-life of 5500 h for NDMA in sediment at 25 °C (DMER & AEL, 1996). Factors that slow degradation include anoxic conditions and lack of illumination, the former by preventing the generation of oxidants and the latter by preventing photolysis and the generation of oxidants by photolytic processes.

5.4 Soil

On soil surfaces, photolysis and volatilization rapidly remove NDMA. Oliver (1979) reported that 30–80% of an unreported concentration of NDMA volatilized from the soil within the first few hours of application to the soil surface. Once incorporated into subsurface soil, however, NDMA will be highly mobile, with the potential to migrate into groundwater supplies. Subsurface biodegradation is slightly slower under anaerobic than under aerobic conditions (ATSDR, 1989). Soil type only slightly affects biodegradation of NDMA. Aeration of soil improved biodegradation compared with waterlogged soil. Pre-exposure of bacteria to NDMA increased biodegradation in soil (Mallik & Tesfai, 1981). Modelling of environmental partitioning (section 5.6) is based on a mean half-life of 1700 h for NDMA in soil at 25 °C (DMER & AEL, 1996).

5.5 Biota

Although NDMA is not present in plants under natural conditions, it can be taken up from the growth medium. Lettuce and spinach plants absorb NDMA from sand, soil, and water after exposure for 2 days to concentrations ranging from 10 to 100 mg NDMA/kg wet weight, with 3.25% and 0.38% being taken up from the growth medium by lettuce and spinach plants, respectively (Dean-Raymond & Alexander, 1976).

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A bioconcentration factor of 0.2 has been estimated for NDMA (Bysshe, 1982). However, conventional estimates of bioconcentration factors (correlation with K_{ow}) are precluded, since, generally, biota can biotransform NDMA (OME, 1998).

5.6 Environmental partitioning

Fugacity modelling provides an overview of key reaction, intercompartment, and advection (movement out of a system) pathways for NDMA and its overall distribution in the environment. A steady-state, non-equilibrium model (Level III fugacity model) was run using the methods developed by Mackay (1991) and Mackay & Paterson (1991). Values for physical/chemical properties utilized in the modelling are presented in Table 1; those for half-lives in various media are presented in sections 5.1–5.4 above. Modelling was based on an assumed default emission rate of 1000 kg/h into a region of 100 000 km^2, which includes a surface water area (20 m deep) of 10 000 km^2. The height of the atmosphere was assumed to be 1000 m. Sediments and soils were assumed to have an organic carbon content of 4% and 2% and a depth of 1 cm and 10 cm, respectively. The estimated per cent distribution predicted by this model is not affected by the assumed emission rate.

Modelling predicts that when NDMA is continuously released into a medium, most of it will be present in that medium at steady state. For example, if NDMA is discharged into water, almost all of it will be present in the aqueous phase, with very small amounts in air and soil. Almost all of the NDMA is removed by reaction in water. Similarly, most NDMA released to air will exist in the atmosphere, with very small amounts in soil and water. Finally, when NDMA is discharged continuously to soil, almost all of the substance is transported to surface water, and about a third goes into the atmosphere. However, since NDMA is much more persistent in soil than in water or air at steady state, almost all of the NDMA is present in soil, with very little in surface water, and even less in the atmosphere (DMER & AEL, 1996).

In summary, the Level III fugacity model predicts that if NDMA is emitted into water or air, it will be found in, and react in, the medium of discharge. Emission of NDMA into water or air will tend to result in localized contamination of short duration. If emitted to soil, NDMA moves to the water or air compartments, where it undergoes reaction, or it reacts slowly in the soil. Because rates of volatilization, adsorption, runoff, and reaction in soil are relatively slow compared with reaction in air and water, the persistence of NDMA emitted to soil is longer, and there is potential for NDMA to move into the groundwater compartment (DMER & AEL, 1996).

6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

Data primarily on concentrations in the environment from the source country of the national assessment on which the CICAD is based (i.e., Canada) are presented here as a basis for the sample risk characterization. Patterns of exposure in other countries are expected to be similar, although quantitative values may vary.

6.1 Environmental levels

6.1.1 *Ambient air*

There is little information on the presence or concentrations of NDMA in ambient (i.e., outdoor) air in Canada or elsewhere. Limited Canadian data are restricted to the province of Ontario, where short-term measurements have been taken in the immediate vicinity of potential point sources of discharge to the atmosphere, for comparison with background measurements from other urban locations. No data on airborne concentrations at rural locations were identified.

At industrial and urban locations in Ontario in 1990, based on seven samples taken in five cities, concentrations of NDMA were all below the detection limit (detection limits ranged from 0.0034 to 0.0046 μg/m^3).[1]

In surveys during 1990 of ambient air in the vicinity of a chemical production facility in Elmira, Ontario, concentrations of NDMA in 41 samples ranged from not detected (detection limits ranged from 0.0029 to 0.0048 μg/m^3) to 0.230 μg/m^3; concentrations in 20 of the 41 samples were at or above the detection limit.[1] The highest concentrations were measured within the perimeter of the production facility, while the maximum concentration measured beyond this perimeter was 0.079 μg/m^3. Concentrations of NDMA in samples taken

[1] Technical memorandum from A. Ng to G. De Brou dated 27 April 1990 regarding the Elmira (1990) survey: Results of the mobile TAGA; with covering memorandum dated 5 May 1990 from L. Lusis to E. Piché regarding the Elmira NDMA survey report, April 1990. Toronto, Ontario, Ontario Ministry of the Environment.

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in the vicinity of an industrial site in Kitchener, Ontario, were similar.[1]

6.1.2 Indoor air

Available data indicate that levels of NDMA were elevated in indoor air contaminated with environmental tobacco smoke (ETS) in the USA (Brunnemann & Hoffmann, 1978) and Austria (Stehlik et al., 1982; Klus et al., 1992). The maximum concentration of NDMA in ETS-contaminated indoor air was 0.24 $\mu g/m^3$, whereas NDMA was not detected (i.e., <0.003 $\mu g/m^3$) when the indoor air of a residence of a non-smoker was sampled in the same manner (Brunnemann & Hoffmann, 1978). Concentrations of NDMA in ETS-contaminated indoor air in these countries were generally between 0.01 and 0.1 $\mu g/m^3$ (Health Canada, 1999).

6.1.3 Water

Releases of NDMA to water in Canada have been measured primarily in Ontario and vary considerably. As an example, in 1996, a chemical plant released wastewater containing NDMA into the St. Clair River at a concentration of 0.266 µg/litre (Environment Canada, 1997). In April 1997, concentrations of NDMA at the point of release to surface water ranged from 0.096 to 0.224 µg/litre for this company. These concentrations are expected to decrease, as the company installed a wastewater treatment plant in1998.

In a survey of sewage treatment plant effluent in Ontario in 1990, NDMA was detected in 27 of 39 samples, with the maximum concentration being 0.22 µg/litre (OME, 1991).

In 390 samples of raw surface water from 101 water treatment plants sampled for NDMA in Ontario from 1990 to July 1998, concentrations were detectable (>0.001 µg/litre) in the raw water at 37 plants. The average concentration in raw water was 1.27×10^{-3} µg/litre. The highest concentration of NDMA in raw water was 0.008 µg/litre from two water treatment plants in 1996 (Ontario Ministry of Environment and Energy, unpublished data, 1996; P. Lachmaniuk, Ontario Ministry of the Environment, unpublished data, 1998).

In 1990, concentrations of NDMA in 24 groundwater samples taken from various locations in Ontario were below detection limits (detection limits ranged from 0.001 to 0.010 µg/litre). Concentrations of NDMA in the municipal aquifer in Elmira ranged from 1.3 to 2.9 µg/litre, attributed to contamination from a nearby chemical facility (Kornelsen et al., 1989). The municipal wells using this aquifer were closed in 1989 (Ireland, 1989). In 1994 and 1995, concentrations of up to 0.005 µg NDMA/litre (detection limit 0.001 µg/litre) in raw surface water and groundwater supplies in rural areas in southern Ontario were reported (OME, 1991).

In 313 samples of treated water analysed from 100 locations within Ontario between 1994 and 1996, NDMA was detected (i.e., at greater than 0.001 µg/litre) in at least one sample at 40 of these 100 sites. The censored mean concentration was 0.0027 µg/litre. The highest concentrations were measured in samples from drinking-water plants using a specific pre-blended polyamine/alum water treatment coagulant (Ontario Ministry of Environment and Energy, unpublished data, 1996). These included a concentration of 0.04 µg/litre at the water treatment plant in Huntsville, Ontario. NDMA was detected in all (i.e., at greater than 0.001 µg/litre) 20 samples collected from four water treatment plants using the specific coagulant. The mean concentration of NDMA in these 20 samples was 0.012 µg/litre, whereas the (censored) mean concentration in the remaining 293 samples for the locations where the specific coagulant was not used was 0.002 µg/litre.

Treatment studies on groundwater at a chemical plant in southern Ontario indicated that activated sludge can accumulate NDMA, particularly when nitrification and denitrification are applied to increase the age of the sludge. Concentrations of NDMA sampled in activated sludge ranged from 5 to 10 mg/litre (J. Kochany, personal communication, 1999; E. McBean, personal communication, 1999). In the USA, NDMA has been reported to be a common constituent of sewage sludge. Concentrations ranged from 0.6 to 45 µg/g in the dried sludge from 14 of 15 cities (Mumma et al., 1984).

6.1.4 Sediment and soil

No data on concentrations of NDMA in sediments or soils in Canada were identified. Levels of NDMA up to 15.1 ng/g have been measured in soils collected in the vicinity of industrial facilities in the USA (IARC, 1978).

6.1.5 Human tissues

NDMA has been quantified in a variety of tissues and biological fluids. In a study conducted in Quebec,

[1] Technical memorandum from A. Ng to M. Lusis dated 24 July 1992, regarding the Kitchener (1992) survey: NC Rubber Products Inc. — Results of the mobile TAGA 6000; with covering memorandum dated 28 July 1992, from M. Lusis to D. Ireland regarding the mobile TAGA 6000 survey of NC Rubber Products Inc. Toronto, Ontario, Ontario Ministry of the Environment.

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Canada, Cooper et al. (1987) detected NDMA in the liver, kidneys, brain, and pancreas from four (non-occupationally exposed) individuals at postmortem; concentrations ranged from approximately 0.12 to 0.9 ng/g tissue. In studies conducted outside of Canada, reported levels of NDMA in the blood or plasma of non-occupationally exposed individuals have ranged from approximately 0.03 to 1.5 ng/ml (Fine et al., 1977; Lakritz et al., 1980; Yamamoto et al., 1980; Garland et al., 1982; Gough et al., 1983; Dunn et al., 1986). In other studies, concentrations of NDMA in breast milk ranged from 0.1 to 1.8 ng/g (Lakritz & Pensabene, 1984; Mizuishi et al., 1987; Uibu et al., 1996). NDMA has been detected in the urine of individuals having no clearly defined exposure to this nitrosamine; reported concentrations from studies conducted in Canada (Kakizoe et al., 1979) and elsewhere (Lakritz et al., 1982; Webb et al., 1983) have ranged from 0.02 to 0.2 ng/ml.

6.1.6 Food

NDMA can be formed during food processing, preservation, and/or preparation from precursor compounds already present in, or added to, the specific food items. The foodstuffs that have been most commonly contaminated with NDMA can be classified into several broad groups:

- foods preserved by the addition of nitrate and/or nitrite, such as cured meat products (in particular, bacon) and cheeses (since these methods of preservation introduce nitrosating species into the food);
- foods preserved by smoking, such as fish and meat products (since oxides of nitrogen in the smoke act as nitrosating agents);
- foods dried by combustion gases, such as malt, low-fat dried milk products, and spices (since combustion gases can contain oxides of nitrogen);
- pickled and salt-preserved foods, particularly pickled vegetables (since microbial reduction of nitrate to nitrite occurs); and
- foods grown or stored under humid conditions, leading to nitrosamine formation by contaminating bacteria.

It should be noted, however, that most data on levels of NDMA in foodstuffs have been derived from studies conducted in the 1970s and 1980s and may not be reliable with respect to estimating current exposure to this substance, owing to the analytical methodology available at the time. Moreover, efforts have been made to reduce the potential for exposure to NDMA in foodstuffs in Canada and other countries through continued reduction of allowable nitrite levels during preservation, suspension of the use of nitrate for certain food groups, or increased use of nitrosation inhibitors, such as ascorbate or erythorbate (Cassens, 1997; Sen & Baddoo, 1997). For example, in Canada, in regulations amended in 1975, permissible levels of nitrite in cured meat products were lowered and the use of nitrate was eliminated, except for a few classes of products (including "slow-cured" meats) (G. Lawrence, personal communication, 1999). The use of nitrate in seafood preservation was suspended in 1965.[1]

Data concerning the concentrations of NDMA in food items in Canada from each of the groups in which there is potential for exposure are limited and largely predate the introduction of controls outlined above. Concentrations of NDMA in 121 samples of various meat products in Canada ranged from less than 0.1 µg/kg (the limit of detection) to a maximum of 17.2 µg/kg in a sample of bacon (Sen et al., 1979, 1980b). Concentrations of NDMA in 63 samples of various fish and seafood products in Canada ranged from less than 0.1 µg/kg (the limit of detection) to a maximum of 4.2 µg/kg in a sample of salted/dried fish (Sen et al., 1985). Concentrations of NDMA in 62 samples of cheese (31 of Canadian origin and 31 imported) purchased in Canada ranged from less than 1 µg/kg (the limit of detection) to a maximum of 68 µg/kg in a sample of wine cheese (Sen et al., 1978).

NDMA was generally not detected in samples of milk products, except for skim milk powder, where it was present in all 11 samples, at a maximum concentration of 0.7 µg/kg (Sen & Seaman, 1981b). In other countries, the presence of NDMA in non-fat dried milk powders has been attributed to the use of natural gas for direct fired heating (Kelly et al., 1989; Scanlan et al., 1994). In Canada, in other foods dried directly, NDMA was detected in 1 of 10 samples of instant coffee at a concentration of 0.3 µg/kg and in 2 of 20 samples of dried soup with a maximum concentration of 0.25 µg/kg (Sen & Seaman, 1981b).

NDMA was not detected (at limits of detection ranging from 0.1 to 0.5 µg/kg) in 25 samples of baby food, including formula, cereal, and mixed food containing meat, analysed from 1979 to 1981 (Sen et al., 1979, 1980b; Sen & Seaman, 1981b). In a survey of other food products in 1979, NDMA was not detected in apple juice or drink, ketchup and other sauces, Ovaltine, margarine,

[1] Internal memorandum dated 13 September 1999 from J. Salminen, Bureau of Chemical Safety, Food Directorate, to B. Meek, Bureau of Chemical Hazards, Environmental Health Directorate, Health Canada, Ottawa, Ontario (File No. FP99072001-597).

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butter, lard, or (fresh and canned) mushrooms (Sen et al., 1980b). The limit of detection was 0.1 µg/litre or 0.1 µg/kg. NDMA was detected at a trace level (<0.2 µg/kg) in 1 of 11 samples of pizza and pizza toppings (Sen et al., 1980b).

Among the cured meat products analysed, bacon was unique, in that it was generally free of nitrosamines in the raw stage. Nitrosamines were formed in bacon only during high-heat frying (Sen et al., 1979). Various factors control the formation of NDMA in fried bacon, including the initial and residual levels of nitrite, processing conditions, the diet of the pigs, the lean to adipose tissue ratio, the presence of inhibitors, frying temperatures, and cooking methods (Sen, 1986). The cooked-out fat contains higher (approximately twice as high) levels of nitrosamines than the cooked lean bacon, and steam-volatile nitrosamines such as NDMA are volatilized in the fumes produced during frying (Sen, 1986).

Concentrations of NDMA in bacon currently consumed in Canada are unlikely to be as high as the maximum of 17.2 µg/kg reported previously (Sen et al., 1979, 1980b), as a result of the introduction of controls on the use of nitrate and nitrite in cured meat products in 1975. However, quantitative data are not available to support this conclusion.

There is consensus among the literature surveyed that concentrations of NDMA in foods from developed countries were an order of magnitude lower in the late 1980s and1990s than in the 1970s (Tricker et al., 1991a; Cornée et al., 1992; Sen et al., 1996). The reduction in the concentrations of preformed NDMA in foods is attributed to improvements in food cooking and preservation techniques. However, no data are available with which to determine whether the concentrations of preformed NDMA in foods in Canada or elsewhere have continued to decline throughout the 1990s or remain at the levels measured in the late 1980s and 1990s.

Most malt beverages, including beer and most brands of whiskey, regardless of origin, contain NDMA (ATSDR, 1989). The presence of NDMA in beer was first reported in 1977 (Sen et al., 1980a; OME, 1991). Malt was found to be the main source of NDMA contamination in beer, and NDMA was shown to be formed during direct drying of malt using hot flue gases — a practice that was common prior to 1980 (Spiegelhalder et al., 1980). Improved malt drying techniques (direct to indirect in 1981) have now significantly reduced the levels of NDMA in malt and beer (OME, 1991; Sen et al., 1996). It is currently believed that NDMA is only a minor component of the total *N*-nitroso compounds in beer and that the major contribution is made by as yet unidentified non-volatile *N*-nitroso compounds (Massey et al., 1990; UK MAFF, 1992). Among samples of beer produced in Canada, a maximum concentration of 4.9 µg/litre was reported in a beer from Ontario in 1978, while in more recent samples (i.e., 1988–1989), the maximum concentration was 0.59 µg/litre. Among imported beers purchased in Canada, a maximum concentration of 9.2 µg/litre was reported in a beer sampled in 1991–1992, while in more recent samples (i.e., October–December 1994), the maximum concentration was 3.2 µg/litre.

NDMA may also be endogenously produced *in vivo* from precursor compounds contained in the food ingested (e.g., DMA in meats and fish and nitrate/nitrite in vegetables) and/or already present in the human body (e.g., nitrate, nitrite) (Vermeer et al., 1998). However, available data are inadequate to serve as a basis for determining the quantities of endogeneous NDMA formed or their relative contribution to exposure via ingestion compared with that from the exogenous presence of NDMA in food (Cornée et al., 1992).

6.1.7 Consumer products

Exposure can result from the use of consumer products that contain NDMA, such as cosmetics and personal care products, products containing rubber, and tobacco products.

NDMA has been detected in a variety of personal care and cosmetic products (e.g., shampoos, hair conditioners and toners, bath and shower gels, creams and oils, face tonics, cleansers), likely due to the reaction of nitrosating agents such as nitrite and/or nitrogen oxides, which occur frequently therein (Spiegelhalder & Preussmann, 1984), with amine-containing compounds, which are used extensively in ingredients of personal care products. Examples include surfactants, detergents, foam boosters, protein additives, and colouring agents (ECETOC, 1990). Nitrosation of precursor compounds in cosmetic matrices, which likely include quaternary ammonium compounds, betaines, and amine oxides (ECETOC, 1991), is often slow, but cosmetic products may remain on store shelves and in consumers' cabinets for extended periods of time, during which nitrosamines can continue to form in the products (Havery & Chou, 1994).

Fifty (or 34.5%) of 145 products surveyed in Germany in 1984 contained NDMA, at a maximum concentration of 24 µg/kg in one shampoo (Spiegelhalder & Preussmann, 1984). In some countries, controls have been introduced to limit levels of nitrosamines in cosmetics. For example, in Canada, manufacturers who

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submit cosmetic notifications for formulations that include combinations of such precursor substances are requested to provide evidence that the level of nitrosamines present in the product or formed over a period equivalent to the shelf life of the product does not exceed 10 µg/kg. Failing this, manufacturers are required to reformulate the products to remove either the amines/amides or the nitrosating agents (R. Green, personal communication, 1995).

Rubber-containing products that come into contact with human skin are another potential source of exposure to NDMA, since dialkylamines used in rubber vulcanization as accelerators and stabilizers can react with nitrosating agents to form nitrosamines (Biaudet et al., 1997). NDMA has been detected in a diverse selection of workplace, consumer, and medical products containing rubber (Health Canada, 1999). The maximum concentration of NDMA detected (i.e., 329 mg/kg) was in latex disposable protective gloves in the USA. However, only a small proportion of the total nitrosamines in the gloves would be expected to be leached out and dermally absorbed (Fiddler et al., 1985). *N*-Nitrosamines have been detected in baby bottle rubber nipples and pacifiers in Canada. The maximum concentrations of NDMA reported in the published literature were 25 mg/kg in baby bottle rubber nipples and 8.6 mg/kg in rubber pacifiers (Sen et al., 1984).

The nitrosation of natural constituents of tobacco during curing and fermentation results in the formation of three major classes of *N*-nitroso compounds in tobacco and tobacco products — volatile, non-volatile, and tobacco-specific *N*-nitrosamines (Hoffmann et al., 1984; Tricker et al., 1991b). In addition, the combustion of cigarette tobacco results in the pyrolytic formation of volatile *N*-nitrosamines, including NDMA (Tricker & Preussmann, 1992). The yields of these volatile *N*-nitrosamines in cigarette smoke from combustion of tobacco depend on many chemical and physical parameters, including the amounts of organic nitrogen and nitrate present (Hoffmann et al., 1987). Furthermore, nicotine serves as a specific precursor for formation of NDMA (Hoffmann et al., 1987).

The NDMA content of cigarette and oral tobacco and the amounts of NDMA in mainstream smoke, sidestream smoke, and ETS have been assessed in several studies (Health Canada, 1999). The levels of preformed volatile *N*-nitrosamines in the cigarette tobacco are considerably lower than the corresponding levels in the mainstream smoke (Tricker et al., 1991b), and the levels of NDMA in sidestream smoke are generally 1 or 2 orders of magnitude greater than in the mainstream smoke from the same cigarette (Health Canada, 1999).

The average ETS emission factor for NDMA for six US commercial cigarette brands was 570 ± 120 ng/cigarette (Daisey et al., 1994; Mahanama & Daisey, 1996). These data have been extrapolated to estimate the concentration of NDMA in indoor air spaces of defined volume and air exchange rates. The predicted concentrations of NDMA in indoor air ranged from 0.002 to 0.005 mg/m^3 (Mahanama & Daisey, 1996). Predicted concentrations based on data from other studies ranged from 0.011 to 0.037 mg/m^3 (Mahanama & Daisey, 1996). These modelled concentrations are similar to the measured concentrations of NDMA in indoor air contaminated with ETS, summarized in section 6.1.2.

6.2 Human exposure: environmental

Point estimates of daily intake (per kilogram body weight), based on available data that are limited in both spatial and temporal scope and reference values for body weight, inhalation volumes, and amounts of food and drinking-water consumed daily, are presented for six age groups in Table 2. These are ranges of reasonable worst-case estimates of daily intake, based on historic data, and indicate that daily intake of NDMA may be as high as 0.03 µg/kg body weight per day. It is not possible to develop defensible estimates of the current average daily intakes of NDMA for the general population due to the limitations of the (particularly recent) available Canadian data. If, despite these limitations, the lower ends of the ranges of reasonable worst-case estimates are considered upper bounds of average population exposure estimates, the daily intake of NDMA from outdoor air (in the vicinity of point sources), water, and food for the general population is unlikely to exceed 0.008 µg/kg body weight per day. Based on the assumptions underlying the reasonable worst-case estimates, most of the daily intake can be attributed to consumption of food contaminated with NDMA during processing, preservation, and/or preparation. It should be noted, though, that the data on which the estimates in food are based may not be representative of the situation today, due to the impact of subsequent introduction of changes in food processing and controls to limit formation in food. Intake of NDMA due to inhalation of air contaminated by atmospheric discharges from industrial point sources contributes somewhat less to the total daily intake,[1] and an even smaller contribution is attributed to consumption of drinking-water containing NDMA, based on a survey of

[1] Since NDMA was not detected in the one available survey of air not impacted by industrial point sources (i.e., Windsor, Ontario) (Ng & Karellas, 1994b), data were considered inadequate as a basis for estimation of the intake of NDMA in ambient air by the general population residing in an urban area, without point sources.

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Table 2: Reasonable worst-case estimates of daily intake of NDMA by the general population in the sample country.

Media	Reasonable worst-case estimates of daily intake of NDMA (µg/kg body weight per day)					
	0–0.5 years[a]	0.5–4 years[b]	5–11 years[c]	12–19 years[d]	20–59 years[e]	60+ years[f]
Air[g]	0.0005–0.005	0.001–0.011	0.0008–0.009	0.0004–0.005	0.0004–0.004	0.0003–0.004
Water[h]	0.0013–0.004	0.0006–0.002	0.0004–0.001	0.0002–0.001	0.0003–0.001	0.0003–0.001
Food[i,j]	0.0004–0.001[k]	0.0065–0.016	0.0045–0.011	0.0036–0.009	0.0043–0.011	0.0036–0.009
Subtotals	0.0022–0.010[l]	0.0081–0.029	0.0057–0.021	0.0042–0.015	0.005–0.016	0.0042–0.014
Indoor air–ETS[m]	0.06	0.13	0.10	0.06	0.05	0.04
Groundwater[n]	0.14–0.31	0.06–0.13	0.05–0.10	0.03–0.06	0.03–0.06	0.03–0.06
Beer[o]				<0.0002	0.0009	<0.0004
Shampoo[p]				0.00002	0.00002	0.00002

[a] Assumed to weigh 7.5 kg, to drink 0.8 litres/day of total tap water (as infant formula), and to breathe 2.1 m³ of air per day (EHD, 1998).

[b] Assumed to weigh 15.5 kg, to drink 0.7 litres/day of total tap water, and to breathe 9.3 m³ of air per day (EHD, 1998).

[c] Assumed to weigh 31.0 kg, to drink 1.1 litres/day of total tap water, and to breathe 14.5 m³ of air per day (EHD, 1998).

[d] Assumed to weigh 59.4 kg, to drink 1.2 litres/day of total tap water, and to breathe 15.8 m³ of air per day (EHD, 1998).

[e] Assumed to weigh 70.9 kg, to drink 1.5 litres/day of total tap water, and to breathe 16.2 m³ of air per day (EHD, 1998).

[f] Assumed to weigh 72.0 kg, to drink 1.6 litres/day of total tap water, and to breathe 14.3 m³ of air per day (EHD, 1998).

[g] These reasonable worst-case estimates of intake by inhalation are based on short-term measurements of NDMA in outdoor air in the close vicinity of point sources of atmospheric discharge in Ontario. The minimum estimates are based on the lowest limit of detection (i.e., 0.0017 µg/m³) for half-hour averaging times for Trace Atmospheric Gas Analyser (TAGA) measurements of NDMA in Kitchener, Ontario, in 1992 (technical memorandum from A. Ng to M. Lusis dated 24 July 1992 regarding the Kitchener (1992) survey: NC Rubber Products Inc. — Results of the mobile TAGA 6000; with covering memorandum dated 28 July 1992 from M. Lusis to D. Ireland regarding the mobile TAGA 6000 survey of NC Rubber Products Inc.; Toronto, Ontario, Ontario Ministry of the Environment). The maximum estimates are based on the censored mean concentration (i.e., 0.019 µg/m³) for half-hour averaging times for TAGA measurements of NDMA (n = 74) in Elmira and Kitchener, Ontario (technical memorandum from A. Ng to M. Lusis dated 24 July 1992 [see above]; technical memorandum from A. Ng to G. De Brou dated 27 April 1990 regarding the Elmira (1990) survey: Results of the mobile TAGA; with covering memorandum dated 5 May 1990 from L. Lusis to E. Piché regarding the Elmira NDMA survey report, April 1990; Toronto, Ontario, Ontario Ministry of the Environment). Concentrations equivalent to one-half the appropriate limits of detection were assumed for half-hour averages during which NDMA was not detected. It was assumed that the population would be exposed to similar concentrations for 24 h daily, and that concentrations in the indoor air would be the same as those in outdoor air, in the immediate vicinity of the point sources.

[h] These reasonable worst-case estimates of intake by ingestion of drinking-water are based on concentrations of NDMA measured in drinking-water in Ontario. The minimum estimates are based on the mean concentration (i.e., 0.012 µg/litre) for 20 samples from four water treatment plants in Ontario where elevated concentrations of NDMA were attributed to the use of a pre-blended polyamine/alum product in the water treatment plant (Ontario Ministry of Environment and Energy, unpublished data, 1996). The maximum estimates are based on the maximum concentration (i.e., 0.04 µg/litre) among these 20 samples, measured at the water treatment plant in Huntsville, Ontario (Ontario Ministry of Environment and Energy, unpublished data, 1996).

[i] Daily consumption rates (i.e., grams/person per day) of 181 food items by six age groups of Canadians (EHD, 1998) are the basis for the calculation of the reasonable worst-case daily intake of NDMA from ingestion of foods. In Canada, NDMA has been detected in 10 food items for which these daily consumption rates are available. (Intakes from an 11th food item [i.e., beer] are not included in these intake estimates.) The maximum concentrations of NDMA reported for each of the 10 food items (Sen et al., 1978, 1979, 1980b, 1985) were selected for calculation of the maximum estimates of intake from foods for the six age groups. Concentrations of NDMA in the remaining 171 food items were assumed to be zero.

[j] The maximum concentrations in each of the 10 food items (i.e., referred to in footnote i) were reduced in proportion to the frequencies of detection of NDMA in the food item for calculation of the minimum estimates of intake from foods for the six age groups (EHD, 1998). The number of samples of each of the 10 food items referred to in footnote i ranged from 2 (for cottage cheese) to 55 (for cured pork). The frequencies of detection of NDMA in the 10 food items were calculated and ranged from 25% to 100%. Concentrations of NDMA in the remaining 171 food items were assumed to be zero.

[k] The estimates of intake of NDMA by infants were based on the assumption that these infants consume table-ready foods at rates indicated in EHD (1998).

[l] The total daily intake of NDMA by infants is overestimated, since the infants are assumed to be consuming both formula (i.e., reconstituted with drinking-water) and table-ready foods on a daily basis.

[m] Based on the assumption that the population spends 21 h/day (EHD, 1998) breathing ETS-contaminated indoor air containing NDMA at the maximum reported concentration (0.24 µg/m³) measured in a bar in the USA (Brunnemann & Hoffmann, 1978).

[n] Based on the minimum (1.3 µg/litre) and maximum (2.9 µg/litre) concentration of NDMA in well water in Elmira, Ontario (Kornelsen et al., 1989), resulting from contamination of groundwater by a nearby industrial facility, and average daily rates of water consumption (EHD, 1998).

[o] Based on the most recent maximum concentration (0.59 µg/litre) of NDMA in Canadian beer (Sen et al., 1996) and average daily rates of intake of beer from EHD (1998). Intake from imported beer may be higher.

[p] Dermal intake only. These estimates are based on the Canadian regulatory limit (i.e., 10 µg/kg) for nitrosamines in personal care products (R. Green, personal communication, 1995). Shampoo was selected, as the maximum reported concentration of NDMA (24 µg/kg) in such products has been in shampoo in Germany (Spiegelhalder & Preussmann, 1984). Dermal intake was estimated by a generalized approach involving product use scenarios (ECETOC, 1994).

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water treatment plants in Ontario. However, although possibly unrepresentative, available data indicate that contaminated groundwater in the vicinity of industrial point sources can, in some cases, lead to intakes that are greater than those from all other media combined.

If it is assumed that the population is exposed to the maximum concentration of NDMA in ETS-contaminated indoor air (0.24 μg/m^3) for 21 h/day (EHD, 1998), the upper-bounding estimates of intake by inhalation range from 0.04 to 0.13 μg/kg body weight per day. If it is assumed that an average adult smoker consumes 20 cigarettes a day and that the mainstream smoke contains between 4 and 278 ng/cigarette (Adams et al., 1987; Kataoka et al., 1997), the estimated intake of NDMA is 0.080–5.6 μg/smoker per day, or 0.001–0.08 μg/kg body weight per day. The upper end of this range of estimates of daily intake for smokers (i.e., 0.08 μg/kg body weight per day) is 5 times greater than the upper end of the range of reasonable worst-case estimates of intakes for adults from air, water, and food (i.e., 0.016 μg/kg body weight per day, as summarized in Table 2).

Reasonable worst-case estimates of daily intake of NDMA for all age groups from ingestion of contaminated groundwater range from 0.03 to 0.31 μg/kg body weight per day (see Table 2). These estimates are based on the minimum (i.e., 1.3 μg/litre) and maximum (i.e., 2.9 μg/litre) confirmed concentrations of NDMA in supply wells in Elmira, Ontario, in 1989 (Kornelsen et al., 1989). The groundwater was contaminated by discharges from a nearby industrial facility.

Estimates of daily intake of NDMA from ingestion of beer are not included in the reasonable worst-case estimates of intake from food in Table 2. For comparison, the most recent maximum concentration (i.e., 0.59 μg/litre) of NDMA in Canadian beer[1] (Sen et al., 1996) and average daily rates of consumption of beer (EHD, 1998) are the basis for reasonable worst-case estimates of daily intake, which range from <0.0002 to 0.0009 μg/kg body weight per day.

Based on the limit (i.e., 10 μg/kg) for nitrosamines in cosmetics in Canada (R. Green, personal communication, 1995), the potential dermal uptake of NDMA from a shampoo was estimated based on product use scenarios (ECETOC, 1994). A shampoo was selected for this calculation, as the maximum reported concentration (i.e., 24 μg/kg) of NDMA in personal care products was in a shampoo in Germany (Spiegelhalder & Preussmann, 1984). The estimated uptake of 0.000 02 μg/kg body weight per day resulting from this calculation (Health Canada, 1999) is several orders of magnitude less than the reasonable worst-case estimates of combined daily intakes from air, water, and food that are summarized in Table 2.

6.3 Human exposure: occupational

Although NDMA is not used directly, workplaces in which there is potential for exposure to NDMA (as a by-product of manufacturing processes) include, but are not necessarily limited to, leather tanneries, rubber and tire industries, rocket fuel industries, dye manufacturers, soap, detergent, and surfactant industries, foundries (core-making), fish processing industries (fish meal production), pesticide manufacturers, and warehouses and sales rooms (especially for rubber products) (ATSDR, 1989). Occupational exposure may result from inhalation or dermal contact (ATSDR, 1989). The National Occupational Exposure Survey (1981–1983) indicated that 747 workers, including 299 women, were potentially exposed to NDMA (NIOSH, 1984) in the USA. US Occupational Safety and Health Administration regulations concerning NDMA (OSHA, 1993) designate strict procedures to avoid worker contact. Mixtures containing >1.0% NDMA must be maintained in isolated or closed systems, workers must observe special hygiene rules, and certain procedures must be followed for movement of the material and in case of accidental spills or emergencies. Synthetic cutting fluids, semisynthetic cutting oils, and soluble cutting oils may contain nitrosamines, either as contaminants in amines or as products from reactions between amines and nitrite. Concentrations of nitrosamines ranging from 1 to 1000 mg/litre have been determined in certain synthetic cutting oils. There are approximately 8–12 additives that could be responsible for nitrosamine formation in cutting oils. Approximately 750 000–780 000 workers employed by more than 1000 cutting fluid manufacturing firms are potentially exposed to nitrosamines in cutting oils. In addition, there is potential exposure of an undetermined number of machine shop workers who use these fluids. Kauppinen et al. (2000) estimated that in the early 1990s, about 14 000 workers in the European Union likely had occupational exposure to NDMA. Based upon monitoring studies conducted in a number of rubber manufacturing facilities in Europe, reported maximum concentrations of NDMA in workplace air have ranged from about 1 μg/m^3 into the hundreds of micrograms per cubic metre (Ducos & Gaudin, 1986; Daubourg et al., 1992; Solionova et al., 1992; Rogaczewska & Wróblewska-Jakubowska, 1996; Oury et al., 1997; Straif et al., 2000).

[1] Intake from imported beer may be higher.

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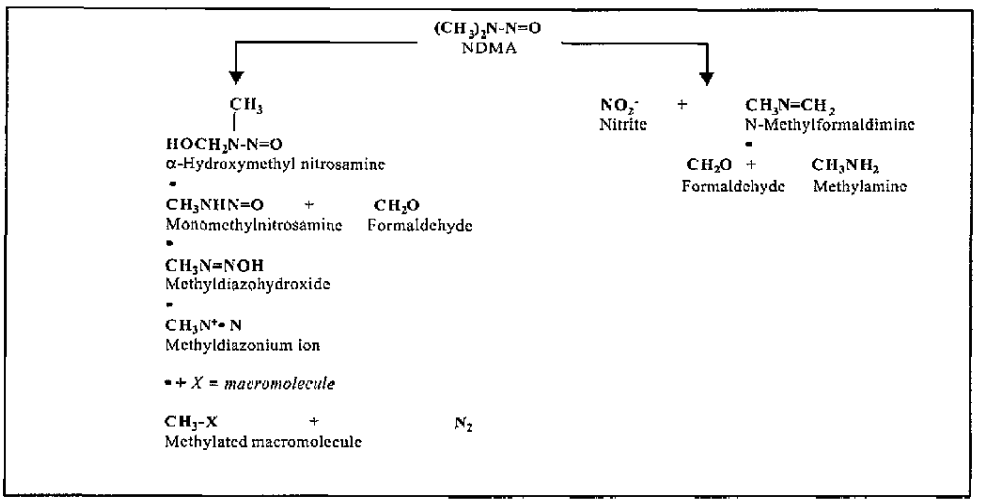

Figure 2: Pathways of NDMA metabolism (adapted from ATSDR, 1989; Haggerty & Holsapple, 1990; Lee et al., 1996).

7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

While quantitative data in humans have not been identified, on the basis of studies conducted with laboratory animals, ingested NDMA is absorbed rapidly and extensively (i.e., >90%) (Daugherty & Clapp, 1976; Diaz Gomez et al., 1977; Kunisaki et al., 1978), primarily from the lower intestinal tract (Phillips et al., 1975; Hashimoto et al., 1976; Agrelo et al., 1978; Pegg & Perry, 1981). Detection of NDMA in the urine of rats and dogs exposed by inhalation indicates that the nitrosamine is absorbed through the lungs; however, reliable quantitative information on the absorption of NDMA following inhalation was not identified. Although quantitative data were not identified, absorption through the skin may be inferred from the results of a study in which small amounts (i.e., 0.03%) of NDMA were detected in the urine of rats following epicutaneous (dermal) administration of a solution containing 350 µg NDMA (Spiegelhalder et al., 1982).

Once absorbed, NDMA and its metabolites are distributed widely (Daugherty & Clapp, 1976; Anderson et al., 1986) and likely passed to offspring through mothers' milk (Diaz Gomez et al., 1986). The nitrosamine and its metabolites have been detected in the fetuses of pregnant rodents injected with the substance (Althoff et al., 1977; Johansson-Brittebo & Tjälve, 1979). Pharmacokinetic analyses of NDMA injected intravenously into a number of laboratory species have revealed that the nitrosamine is cleared rapidly from the blood, with metabolism involving both hepatic and extrahepatic components. NDMA and its metabolites may be excreted in the urine or exhaled as carbon dioxide.

Quantitative information from studies on the metabolism of NDMA in individuals was not identified. However, based upon a few studies in which the metabolic conversion of NDMA in human liver preparations has been examined, there appear to be no qualitative differences in the metabolism of NDMA between humans and laboratory animals. The metabolism of NDMA involves either the • -hydroxylation or denitrosation of the nitrosamine (Figure 2). Both pathways are considered to proceed through a common intermediate radical [$CH_3(CH_2•)N–N=O$], generated by the action of the cytochrome P450 [CYP2E1]-dependent mixed-function oxidase system (Haggerty & Holsapple, 1990; Lee et al., 1996). Along the • -hydroxylation pathway, the hydroxymethylnitrosamine ($HOCH_2CH_3N–N=O$) formed from the intermediate radical decomposes to formaldehyde (itself ultimately converting to carbon dioxide) and monomethylnitrosamine ($CH_3NHN=O$); the monomethylnitrosamine, owing to its instability, undergoes rearrangement to the strongly methylating methyldiazonium ion ($CH_3N^+• N$), which alkylates biological macromolecules such as DNA, RNA, and proteins. Metabolic conversion of the intermediate radical via denitrosation may lead to the formation of methylamine (CH_3NH_2) and formaldehyde.

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8. EFFECTS ON LABORATORY MAMMALS AND *IN VITRO* TEST SYSTEMS

NDMA has been consistently potently carcinogenic in all experimental species examined. Since exposure to NDMA occurs principally through its occurrence as a contaminant in media to which the general population is exposed, this end-point is expected to be limiting; hence, the focus of testing and, as a result, assessment has been carcinogenicity. Other end-points have not been well investigated; available data are considered inadequate as a basis for their meaningful characterization. In addition, exposure in available studies has been restricted primarily to ingestion; hence, meaningful dose–response analyses for other routes of exposure, even for the critical end-point (e.g., carcinogenicity), are precluded.

8.1 Single exposure

NDMA is highly acutely toxic after oral administration to rats, with LD_{50}s ranging from 23 to 40 mg/kg body weight. It is also highly acutely toxic via inhalation; 4-h LC_{50}s are 78 ppm (240 mg/m^3) for rats and 57 ppm (176 mg/m^3) for mice. One day after three dogs were exposed (via inhalation) to 16 ppm (49 mg/m^3) NDMA for 4 h, one had died, and the others were moribund (ATSDR, 1989). In all three species, acute inhalation exposure produced haemorrhagic necrosis in the liver; an increased blood clotting time was reported for the NDMA-exposed dogs (ATSDR, 1989). Following intraperitoneal exposure, LD_{50}s of 43 mg/kg body weight in rats and 20 mg/kg body weight in mice have been reported (IARC, 1978). In other laboratory species, acute exposure to NDMA produced effects in the liver (hepatotoxicity), kidney (tumours), and testes (necrosis of the seminiferous epithelium) (Magee & Barnes, 1962; Schmidt & Murphy, 1966; Hard & Butler, 1970a,b; McLean & Magee, 1970; OME, 1991).

8.2 Irritation and sensitization

Data on the potential of NDMA to induce sensitization and/or irritation were not identified.

8.3 Short- and medium-term exposure

Hepatic effects (i.e., hepatocyte vacuolization, portal venopathy, and necrosis/haemorrhage), often associated with reduced survival, have been observed in a number of mammalian species exposed orally under various conditions (e.g., in rats receiving 1, 3.8, or 5 mg NDMA/kg body weight per day for 30, 7–28, or 5–11 days, respectively; in mice receiving 5 mg/kg body weight per day for 7–28 days; in hamsters receiving 4 mg/kg body weight per day for 1–28 days; in guinea-pigs, cats, and monkeys receiving 1 mg/kg body weight per day for 30 days or 5 mg/kg body weight per day for 5–11 days; in dogs receiving 2.5 mg/kg body weight per day, 2 days/week, for 3 weeks; and in mink receiving 0.32 mg/kg body weight per day for 23–34 days) (summarized from IARC, 1978; ATSDR, 1989).

In addition to effects in the liver, "congestion" in a variety of organs (i.e., kidneys, lung, spleen, and myocardium) has been reported following examination of rats receiving 3.8 mg NDMA/kg body weight per day in the diet for 1–12 weeks (Khanna & Puri, 1966). Gastrointestinal haemorrhage has been observed in rats receiving dietary doses of 10 mg NDMA/kg body weight per day for 34–37 days (Barnes & Magee, 1954) and in mink receiving 0.3 or 0.6 mg NDMA/kg body weight per day in the diet for 23–34 days (Carter et al., 1969). Effects in the kidneys (including glomerulus dilatation and slight thickening of the Bowman's capsule) were observed in mink receiving 0.2 mg NDMA/kg body weight per day from the diet (period not specified) (Martino et al., 1988).

8.4 Carcinogenicity

Although most studies would be considered limited by current standards (e.g., small group sizes, single dose levels, limited histopathological examination), there has been clear, consistent evidence of carcinogenicity in a number of studies in which rodents (i.e., rats, mice, hamsters) were exposed to NDMA orally, via inhalation, or by intratracheal instillation. NDMA increased the incidence of liver and Leydig cell tumours in rats ingesting this nitrosamine from drinking-water or the diet (Terao et al., 1978; Arai et al., 1979; Ito et al., 1982; Lijinsky & Reuber, 1984); increased tumour incidences were noted at concentrations of NDMA of about 5 mg/litre in drinking-water and 10 mg/kg in the diet. Increased incidences of nasal, hepatic, pulmonary, and renal tumours were observed in rats exposed to NDMA via inhalation (Moiseev & Benemanskii, 1975; Klein et al., 1991); increases in the incidence of hepatic, pulmonary, and renal tumours were observed following exposure to NDMA at a concentration of 0.2 mg/m^3 (Moiseev & Benemanskii, 1975). Hepatic, pulmonary, and renal carcinogenicity was observed in mice administered NDMA via drinking-water (Terracini et al., 1966; Clapp & Toya, 1970; Anderson et al., 1979, 1986, 1992) or through inhalation (Moiseev & Benemanskii, 1975); increases in tumour incidence were observed at concentrations of NDMA in drinking-water ranging from 0.01 to 5 mg/litre. Moreover, in some cases (e.g., Terracini et al., 1966), the period of exposure to NDMA was relatively short (i.e., 3 weeks). NDMA increased the incidence of liver tumours in hamsters exposed intratracheally (Tanaka et al., 1988). The administration of NDMA to pregnant rats (by intraperitoneal injection) or mice (by stomach tube) increased the frequency of

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hepatic and renal tumours in the offspring (Alexandrov, 1968; Anderson et al., 1989). An increased incidence of renal tumours has also been observed in rats administered either a single oral (Magee & Barnes, 1962) or intraperitoneal (Hard & Butler, 1970a; McLean & Magee, 1970) dose of NDMA (at levels of 30–60 mg/kg body weight).

In a more recently conducted comprehensive carcinogenicity bioassay (designed to provide detailed information on exposure–response) involving lifetime exposure, 15 dose groups of 60 male and 60 female Colworth-Wistar rats were provided with drinking-water containing a wide range of concentrations of NDMA[1] (Tables 3 and 4) (Brantom, 1983; Peto et al., 1991a,b). The estimated daily intakes of NDMA ranged from 0.001 to 0.697 mg/kg body weight in the males and from 0.002 to 1.224 mg/kg body weight in the females. A control group of 120 males and 120 females received drinking-water without NDMA (Brantom, 1983; Peto et al., 1991a,b). Groups of animals were taken for interim sacrifice after 12 and 18 months of study. Survival of the animals was reduced with increasing dose; animals in the highest dose group did not survive longer than 1 year. There were no significant differences in body weight between the exposed animals and the controls. Dose-related increases in tumour incidence were observed only in the liver in both males and females (see Tables 3 and 4). The increase in tumour incidence was greatest for hepatocellular carcinoma and biliary cystadenoma. Non-neoplastic effects observed in the liver included hyperplastic nodules and the shrinkage of hepatocytes.

8.5 Genotoxicity and related end-points

In numerous studies conducted *in vitro* in bacterial and mammalian cells, there has been overwhelming evidence that NDMA is mutagenic and clastogenic (reviewed in IARC, 1978; ATSDR, 1989). Increased frequencies of gene mutations, chromosomal damage, sister chromatid exchange, and unscheduled DNA synthesis have been observed in a wide variety of cell types, in assays conducted in the presence or absence of metabolic activation. Positive results have been observed in human as well as rodent cells.

Similarly, clear evidence of genetic effects has also been observed in *in vivo* studies. Clastogenic effects (e.g., micronuclei, sister chromatid exchange, chromosomal aberrations) in hepatocytes (Tates et al., 1980, 1983, 1986; Mehta et al., 1987; Braithwaite & Ashby, 1988; Cliet et al., 1989; Neft & Conner, 1989; Sawada et al., 1991), bone marrow cells (Bauknecht et al., 1977; Wild, 1978; Neal & Probst, 1983; Collaborative Study Group for the Micronucleus Test, 1986; Neft & Conner, 1989; Krishna et al., 1990; Sato et al., 1992; Morrison & Ashby, 1994), spleen cells (Neft & Conner, 1989; Krishna et al., 1990), and peripheral blood lymphocytes (Tates et al., 1983; Sato et al., 1992), as well as in oesophageal (Mehta et al., 1987) and kidney cells (Robbiano et al., 1997), have been observed in rodents (rats, mice, or hamsters) administered NDMA either orally or by intraperitoneal injection. Increased frequencies of micronucleated cells were observed at doses as low as 5 mg/kg body weight in rats (Trzos et al., 1978; Mehta et al., 1987). Effects in germ cells (i.e., micronucleated spermatids) were observed in mice given 6 or 9 mg NDMA/kg body weight via intraperitoneal injection (Cliet et al., 1993). The inhalation exposure of female mice to 1030 mg NDMA/m^3 increased the frequency of micronucleated bone marrow cells (Odagiri et al., 1986). Evidence of genotoxicity (e.g., chromosomal aberrations, micronuclei, gene mutation, DNA strand breaks) has also been observed in the offspring of hamsters (Inui et al., 1979) and mice (Bolognesi et al., 1988) administered NDMA during gestation.

In rodents (rats, mice, or hamsters) administered NDMA either orally or by intraperitoneal injection, evidence of DNA damage has been observed in the liver, kidneys, and lungs (Laishes et al., 1975; Petzold & Swenberg, 1978; Abanobi et al., 1979; Mirsalis & Butterworth, 1980; Brambilla et al., 1981, 1987; Bermudez et al., 1982; Cesarone et al., 1982; Barbin et al., 1983; Doolittle et al., 1984; Kornbrust & Dietz, 1985; Loury et al., 1987; Mirsalis et al., 1989; Pool et al., 1990; Brendler et al., 1992; Jorquera et al., 1993; Asakura et al., 1994; Tinwell et al., 1994; Webster et al., 1996). DNA damage in thymus (Petzold & Swenberg, 1978), sperm (Cesarone et al., 1979), and nasal and tracheal cells (Doolittle et al., 1984) has also been noted. NDMA was mutagenic at the *lacI* locus (in the liver) in *in vivo* assays involving transgenic mice (Mirsalis et al., 1993; Tinwell et al., 1994; Butterworth et al., 1998). Effects (i.e., increased unscheduled hepatic DNA synthesis) have been observed in rats at doses as low as 0.1 mg NDMA/kg body weight (Mirsalis & Butterworth, 1980).

[1] The concentrations of NDMA were 33, 66, 132, 264, 528, 1056, 1584, 2112, 2640, 3168, 4224, 5280, 6336, 8448, and 16 896 µg/litre.

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Table 3: Carcinogenicity study with male rats.[a]

Exposure group	NDMA concentration in drinking-water (mg/litre)	Estimated intake (mg/kg body weight per day)[b]	Animals with hepatic tumours (%)[c]		
			Carcinoma	Haemangiosarcoma	Biliary cystadenoma
1	0	0	1	1	1
2	0.033	0.001	2	0	4
3	0.066	0.003	2	0	4
4	0.132	0.005	4	2	4
5	0.264	0.011	2	4	4
6	0.528	0.022	6	0	2
7	1.056	0.044	10	2	2
8	1.584	0.065	13	2	8
9	2.112	0.087	10	13	13
10	2.640	0.109	25	13	23
11	3.168	0.131	29	29	27
12	4.224	0.174	33	21	25
13	5.280	0.218	58	6	29
14	6.336	0.261	60	15	40
15	8.448	0.348	77	6	29
16	16.896	0.697	88	6	4

[a] Brantom (1983); Peto et al. (1991a,b). Animals were provided, for their entire lives until natural death, drinking-water containing the indicated concentrations of NDMA. The animals were sacrificed and necropsied if moribund or exhibiting palpable liver alterations.

[b] Intakes estimated by authors (Peto et al., 1991b).

[c] Proportion of animals with tumours specified at each dose level; $n = 192$ for unexposed controls (treatment group 1); $n = 48$ for each dose level (treatment groups 2–16) (Brantom, 1983).

8.6 Reproductive toxicity

Available data are inadequate as a basis for assessment of the reproductive or developmental toxicity of NDMA. Interpretation of the results of most identified investigations is complicated by the high doses administered, likely to have induced acute or repeated-dose organ toxicity. In a report by Anderson et al. (1978), time to conception in female mice provided with drinking-water containing 0.1 mg NDMA/litre for 75 days prior to mating was about 3 days longer than in unexposed controls; no other reproductive effects were assessed in this study. In a study conducted with male rats, a single intraperitoneal injection of 30 or 60 mg NDMA/kg body weight induced testicular damage (necrosis or degeneration of the seminiferous epithelium) (Hard & Butler, 1970b).

In a single-generation study (Anderson et al., 1978) in which the reproductive effects of a number of substances were examined, groups of 20 female mice were provided with drinking-water containing 0 or 0.1 mg NDMA/litre for 75 days prior to mating and throughout pregnancy and lactation (estimated daily and total intakes of 0.02 mg/kg body weight per day and 2 mg/kg body weight, respectively). The proportion of deaths (based upon the total number of stillborn and neonatal deaths) was increased ($P < 0.05$) 2-fold in the NDMA-exposed animals compared with controls (i.e., 20% and 9.9%, respectively), due in large part to an increase in the number of stillborn animals. Exposure to NDMA had no effect upon maternal fluid consumption, litter size, or average body weight of the weanlings, and no consistent gross or histopathological abnormalities were observed in the stillborn fetuses or dead neonates to account for the increased mortality. In a somewhat more recent study with mice administered higher doses of the nitrosamine, a single intraperitoneal injection of 37 mg NDMA/kg body weight on day 16 or 19 of gestation resulted in the deaths of all fetuses in exposed dams; information on maternal toxicity was not provided (Anderson et al., 1989). Notably, this dose is greater than the LD_{50} for this route in these animals of 20 mg/kg body weight (IARC, 1978). In the same study, lethality was not observed following the administration of 7.4 mg NDMA/kg body weight (Anderson et al., 1989).

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Table 4: Carcinogenicity study with female rats.[a]

Exposure group	NDMA concentration in drinking-water (mg/litre)	Estimated intake (mg/kg body weight per day)[b]	Animals with hepatic tumours (%)[c]		
			Carcinoma	Haemanglosarcoma	Biliary cystadenoma
1	0	0	1	1	2
2	0.033	0.002	0	2	2
3	0.066	0.005	0	0	8
4	0.132	0.010	4	2	0
5	0.264	0.019	4	0	6
6	0.528	0.038	10	2	10
7	1.056	0.076	6	4	15
8	1.584	0.115	10	2	71
9	2.112	0.153	10	6	69
10	2.640	0.191	8	2	83
11	3.168	0.229	13	6	92
12	4.224	0.306	15	4	90
13	5.280	0.382	25	0	85
14	6.336	0.459	38	0	69
15	8.448	0.612	69	6	33
16	16.896	1.224	73	10	8

[a] Brantom (1983); Peto et al. (1991a,b). Animals were provided, for their entire lives until natural death, drinking-water containing the indicated concentrations of NDMA. The animals were sacrificed and necropsied if moribund or exhibiting palpable liver alterations.

[b] Intakes estimated by authors (Peto et al., 1991b).

[c] Proportion of animals with tumours specified at each dose level; $n = 192$ for unexposed controls (treatment group 1); $n = 48$ for each dose level (treatment groups 2–16) (Brantom, 1983).

Fetal body weight was significantly ($P < 0.05$) reduced after a single oral dose of 20 mg NDMA/kg body weight was administered to pregnant rats on day 15 or 20 of gestation (Nishie, 1983). Although information on fetal survival or teratogenicity was not provided, toxic effects (reduced weight gain, hepatotoxicity, and death) were observed among the dams. Fetal deaths were noted in a number of studies (cited in ATSDR, 1989) conducted with rats in which NDMA was administered to pregnant dams 1) as a single oral dose (30 mg/kg body weight) on one of days 1–12 (Alexandrov, 1974) or 1–15 (Napalkov & Alexandrov, 1968) of gestation; 2) as repeated gavage doses of 1.4–2.9 mg/kg body weight per day for 7 or more days during gestation (Napalkov & Alexandrov, 1968); or 3) in the diet (intake of 5 mg/kg body weight per day) from an unspecified day of pregnancy to sacrifice on day 20 of gestation (Bhattacharyya, 1965). Although no teratogenic effects were reported in these studies, interpretation of these investigations is difficult owing to insufficient information on experimental design and results, lack of controls, and lack of information on maternal toxicity (ATSDR, 1989). The doses administered in some of these studies were close to the LD_{50}.

8.7 Neurotoxicity and effects on the immune system

Data concerning effects on the brain or central nervous system in animals exposed to NDMA were not identified.

Similarly, available data are inadequate as a basis for assessment of the immunological effects of NDMA. Interpretation of the results of most identified investigations is complicated by likely toxicity associated with the high doses administered. In studies in which $B6C3F_1$ female mice were administered repeated intraperitoneal injections of 1.5, 3, or 5 mg NDMA/kg body weight per day for 14 days, observed effects on the immune system included suppression of humoral immunity with declines in the IgM antibody-forming cell response to sheep red blood cells and reductions in splenocyte proliferation in response to lipopolysaccharide (reviewed in Haggerty & Holsapple, 1990). Also observed were reductions in T-lymphocyte function (i.e., reduced cell-mediated immunity) with a decline in proliferative responses to various T-cell mitogenic stimuli, suppression of the mixed lymphocyte response, and selected delayed hypersensitivity responses, as well as significant reductions in host resistance to infection with *Listeria monocytogenes*, *Streptococcus zooepidemicus*, or the influenza virus or

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to challenge with B16F10 tumour cells. Reductions in antibody formation and *in vitro* lymphoproliferative responses were observed in male BALB/c mice administered 5 mg NDMA/kg body weight intraperitoneally for 14 days (Jeong & Lee, 1998).

Female CD-1 mice provided with drinking-water containing 5 or 10 mg NDMA/litre for 30–120 days exhibited marked suppression of humoral- and cell-mediated immunity (Desjardins et al., 1992); however, effects were reversible within 30 days of cessation of exposure. No effects were observed in animals consuming drinking-water containing 1 mg NDMA/litre.

8.8 Mode of action

There is strong evidence that the toxicological effects of NDMA are directly dependent upon the CYP2E1-dependent metabolic conversion of this nitrosamine to highly reactive species. Lee et al. (1996) attributed the hepatotoxicity of NDMA to the methyldiazonium ion formed via the • -hydroxylation pathway; denitrosation was considered to make little contribution to the overall hepatotoxic effect of this nitrosamine in rats. The principal DNA adduct formed following exposure to NDMA is N^7-methylguanine (representing about 65% of all adducts formed initially upon exposure); O^6-methylguanine is a secondary adduct (representing about 7% of all adducts formed initially). Other DNA adducts formed in smaller amounts include N^3-methyladenine and O^4-methylthymine.

N^7-Methylguanine may undergo depurination yielding apurinic sites, which, if not repaired prior to DNA replication, can result in guanine to thymine transversions (Swenberg et al., 1991). O^6-Methylguanine and O^4-methylthymine (formed at about 1% of the amount of O^6-methylguanine) are strongly promutagenic by direct mispairing. O^6-Methylguanine gives rise to guanine: cytosine to adenine:thymine (i.e., G:C to A:T) transitions, while O^4-methylthymine causes A:T to G:C transitions (Swenberg et al., 1991; Souliotis et al., 1995).

Available data are consistent with the formation and persistence of the secondary adduct, O^6-methylguanine, being associated with both the carcinogenicity and mutagenicity of NDMA (reviewed in Haggerty & Holsapple, 1990; Swenberg et al., 1991; Souliotis et al., 1995). The ability of cells to repair DNA adducts (by removing O^6-methylguanine through the action of a specific O^6-methylguanine DNA-methyltransferase) prior to cell division likely plays a critical role in determining the susceptibility of tissues to tumour development.

In monkeys administered (orally) 0.1 mg NDMA/kg body weight, O^6-methylguanine was detected in 32 tissues examined (Anderson et al., 1996). The highest levels were in the gastric mucosa and liver, but elevated levels were also present in white blood cells, the oesophagus, ovaries, pancreas, bladder, and uterus. O^6-Methylguanine DNA-methyltransferase activity varied over a 30-fold range; the highest activities were in the gastric mucosa, liver, kidneys, and lungs. The formation of O^6-methylguanine was detected in fetal liver, lung, kidney, spleen, and brain in a study in which pregnant patas monkeys were administered (intragastrically) a single dose of 1 mg NDMA/kg body weight (Chhabra et al., 1995).

The greater persistence of O^6-methylguanine DNA adducts in the kidney compared with the liver in rats administered a single oral dose of 20 mg NDMA/kg body weight parallels earlier findings in which the acute oral or intraperitoneal administration of NDMA to rats at such dose levels increased the incidence of kidney but not liver tumours (Magee & Barnes, 1962; Schmidt & Murphy, 1966; Hard & Butler, 1970a; McLean & Magee, 1970). In contrast, the long-term oral administration of low doses of NDMA (i.e., <2 mg/kg body weight per day) increased the incidence of liver but not kidney tumours in these animals (Brantom, 1983; Lijinsky & Reuber, 1984; Peto et al., 1991a,b), a finding attributed to the first-pass metabolism of NDMA in the liver (Swenberg et al., 1991).

There are quantitative age- and species-related differences in hepatic O^6-methylguanine, possibly associated with variations in the activity of the transferase, consistent with observed variations in the carcinogenicity of the compound among species and strains exposed under various conditions. These include greater hepatic activity in adults versus newborn mice (Coccia et al., 1988), in rats versus mice (Lindamood et al., 1984), and between strains of mice (greater in C3H than in C57BL) (Lindamood et al., 1984).

Evidence supporting a role for O^6-methylguanine formation in tumour development following exposure to NDMA was recently reviewed by Souliotis et al. (1995). G:C to A:T transitions have been observed in the *ras* oncogene in mouse lung tumours induced by NDMA (Devereux et al., 1991), in the livers of *lacI* transgenic mice administered a single dose of 4 mg NDMA/kg body weight (Mirsalis et al., 1993), and in the liver, kidney, and lung of *lacI* transgenic mice administered five daily doses of 1 mg NDMA/kg body weight (Wang et al., 1998). Moreover, transgenic mice expressing high levels of O^6-methylguanine DNA-methyltransferase in the liver were less susceptible than normal controls to NDMA-induced hepatocarcinogenesis (Nakatsuru et al., 1993). However, Souliotis et al. (1995) also reported that the dose–response relationship for the accumulation of O^6-methylguanine in hepatic DNA in rats administered drinking-water (for 28 days) containing concentrations

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of NDMA similar to those used in the study conducted at BIBRA Toxicology International (Brantom, 1983; Peto et al., 1991a,b) did not strictly parallel the dose–response for the development of hepatic tumours in the carcinogenicity bioassay.

9. EFFECTS ON HUMANS

Two deaths linked to the acute ingestion of NDMA, as well as a third attributed to the consumption of at least four doses of approximately 250–300 mg NDMA over a 2-year period, have been reported (Fussgänger & Ditschuneit, 1980; Pedal et al., 1982). Liver failure was observed in all three cases; the two acutely exposed decedents also exhibited cerebral haemorrhage. In two fatalities involving exposure to unknown concentrations of NDMA fumes, a tender and enlarged liver, splenic enlargement, abdominal distension, and the accumulation of yellow fluid in the peritoneal cavity were observed in one man prior to death (Freund, 1937); in the other death, liver cirrhosis was observed at autopsy (Hamilton & Hardy, 1974). In two other non-fatal cases involving exposure to NDMA fumes, effects included jaundice, the accumulation of fluid in the peritoneal cavity, exhaustion, headaches, abdominal cramps, soreness on the left side, nausea, and vomiting (Freund, 1937; Hamilton & Hardy, 1974).

Relevant epidemiological studies include case–control investigations in which the potential risks of cancer of the stomach (Risch et al., 1985; González et al., 1994; La Vecchia et al., 1995; Pobel et al., 1995), upper digestive tract (Rogers et al., 1995), and lung (Goodman et al., 1992; De Stefani et al., 1996) associated with the ingestion of NDMA have been assessed. In some of these reports (Goodman et al., 1992; González et al., 1994; Pobel et al., 1995), the estimated intake of NDMA was based upon recollection of an individual's typical diet consumed in the year preceding the onset of illness, as well as the reported levels of this nitrosamine in the foodstuffs consumed, derived from other studies. In the studies conducted by De Stefani et al. (1996) and Rogers et al. (1995), subjects were asked to recall their typical diet in the 5 and 10 years, respectively, prior to the onset of illness.

In three of four case–control studies,[1] there was a positive relationship with evidence of exposure–response for the intake of NDMA and gastric cancer (González et al., 1994; La Vecchia et al., 1995; Pobel et al., 1995), although not in an additional study in which oral, laryngeal, and oesophageal cancers were investigated separately (Rogers et al., 1995). In two case–control studies[2] in which matching or control for confounders was rather more extensive than that for the investigations of gastric cancer mentioned above, there were clear exposure–response relationships for NDMA and lung cancer (Goodman et al., 1992; De Stefani et al., 1996). In almost all studies, associations between the cancers of interest and nitrate, nitrite, and NDMA were examined; results were relatively consistent in this regard, with there being an association with cancer most commonly with NDMA; results for nitrite were mixed, and there was an inverse association with nitrate.

In a population-based cohort study that assessed the risks of head and neck, stomach, and colorectal cancer associated with the dietary intake of NDMA, the relative risk (RR) of colorectal cancer was increased for

[1] In González et al. (1994), the odds ratios (ORs) for gastric cancer were 1, 1.86, 1.79, and 2.09 among individuals with intakes of NDMA in the first (reference group), second, third, and fourth quartiles, respectively ($P = 0.007$ for trend). Pobel et al. (1995) reported ORs (95% confidence intervals [CIs]) (adjusted for age, sex, occupation, and total caloric intake) of 1, 4.13 (0.93–18.27), and 7.0 (1.85–26.46) among individuals with intakes of NDMA in the first (reference group), second, and third tertiles, respectively ($P = 0.04$ for trend). In La Vecchia et al. (1995), ORs (95% CIs) (adjusted for age, sex, education, family history of gastric cancer, combined food score index, intake of • -carotene, vitamin C, nitrite, nitrate, and total calories) for stomach cancer were 1, 1.11 (0.9–1.4), and 1.37 (1.1–1.7) among individuals with intakes of NDMA in the first (reference group), second, and third tertiles, respectively ($P < 0.01$ for trend).

[2] In Goodman et al. (1992), ORs (95% CIs) (adjusted for age, ethnic group, smoking status, pack-years of cigarette use, and • -carotene intake) for those in the second, third, and fourth quartiles of NDMA intake (compared with the first quartile) were (among men) 1.7 (0.9–3.2), 2.8 (1.4–5.3), and 3.3 (1.7–6.2) and (among women) 1.4 (0.7–2.9), 1.8 (0.7–4.2), and 2.7 (1.0–6.9), respectively (trends were $P = 0.006$ and 0.04 for males and females, respectively). De Stefani et al. (1996) reported ORs (95% CIs) for all types of lung cancer (combined) among individuals in the first, second, third, and fourth quartiles of NDMA intake of 1, 0.88 (0.53–1.48), 1.77 (1.06–2.96), and 3.14 (1.86–5.29), respectively ($P < 0.001$ for trend).

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the group having the highest intake of NDMA[1] (Knekt et al., 1999). The highest intake group had increased and reduced RRs of head and neck (RR = 1.37; 95% CI = 0.5–3.74) and stomach cancer (RR = 0.75; 95% CI = 0.37–1.51), respectively, compared with the lowest quartile (reference group).

There appears to be no qualitative difference between rodents and humans in the formation of DNA adducts following exposure to NDMA. In a case of suspected NDMA poisoning in a human male, methylation of liver DNA was evident at both the N^7 and O^6 positions of guanine (Herron & Shank, 1980). Using an immunohistochemical technique, Parsa et al. (1987) detected the formation of O^6-methylguanine in human pancreatic explants incubated *in vitro* with NDMA.

10. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

10.1 Aquatic environment

Green algae (*Selenastrum capricornutum*) and blue-green algae (*Anabaena flos-aqua*) were exposed to NDMA over a 13-day period in static systems. The test was conducted to determine effects on algal growth rate, cell number, maximum standing crop, and dry weight. The 13-day EC_{50}s for growth were 4 mg/litre and 5.1 mg/litre for the green and blue-green algae, respectively (Draper & Brewer, 1979).

Draper & Brewer (1979) reported a 96-h LC_{50} of 940 mg/litre for fathead minnow (*Pimephales promelas*) and a 96-h LC_{50} of 1365 mg/litre for flatworms (*Dugesia dorotocephala*). For scud (*Gammarus limnaeus*), 96-h LC_{50} values ranged from 280 to 445 mg/litre (Draper & Fisher, 1980). Both studies were conducted in static renewal systems.

The LC_{50} values for a saltwater fish, the common mummichog (*Fundulus heteroclitus*), in a static non-renewal system were 8300 mg/litre at 24 h, 5500 mg/litre at 48 h, 4700 mg/litre at 72 h, 3300 mg/litre at 96 h, and 2700 mg/litre at 120 h (Ferraro et al., 1977).

Grieco et al. (1978) reported a dose-related increase in hepatocellular carcinomas in a study in which rainbow trout (*Oncorhynchus mykiss*) received 3, 200, 400, or 800 mg NDMA/kg in the diet over 52 weeks. Tumours did not form in trout receiving 3 mg/kg, although body weight was reduced. OME (1998) observed that growth reduction in rainbow trout was a more sensitive response than tumour induction.

Frogs (*Rana temporaria*) were exposed to 5 mg NDMA/litre in water for 63 days and 203 days. In both studies, the frogs developed hepatocellular carcinomas as well as adenomas and tumours of the haematopoietic system. Approximately 44% of the frogs exposed for 203 days developed tumours (Khudoley, 1977). In another species of frog (*Xenopus borealis*) exposed for 52 weeks to 400 mg NDMA/litre in aquarium water, 54% of the test animals developed liver and kidney tumours (Khudoley & Picard, 1980). The authors believed that amphibians were more sensitive (shorter latency period and higher tumour incidence) than fish to the carcinogenic effects of the nitrosamine.

11. EFFECTS EVALUATION

11.1 Evaluation of health effects

11.1.1 Hazard identification

Although NDMA is acutely toxic and induces hepatic damage in several species at dose levels of approximately 1 mg/kg body weight per day in short-term experiments, the main concern is its carcinogenicity: NDMA has been consistently shown to be a potent carcinogen in all experimental species studied. Data on other end-points are very limited.

Available data are consistent with the toxicological effects of NDMA being due, in large part, to the alkylation of biological macromolecules (e.g., DNA, RNA, proteins) by the methyldiazonium ion formed during metabolism. Putative pathways for the metabolism of NDMA are similar in rodents and humans.

11.1.1.1 Carcinogenicity

Information relevant to assessment of the carcinogenicity of NDMA has been derived from epidemiological (case–control) studies of the general population, carcinogenesis bioassays involving laboratory animals, and supporting data related to the genotoxicity, metabolism, and interaction of this compound with biological macromolecules.

Although the database is rather limited, data from epidemiological studies are at least suggestive of an

[1] The RRs (95% CIs) (adjusted for age, sex, municipality, smoking, and energy intake) of colorectal cancer among those with intakes of NDMA in the first (reference), second, third, and fourth quartiles were 1, 1.47 (0.69–3.11), 1.95 (0.95–3.99), and 2.12 (1.04–4.33), respectively ($P = 0.47$ for trend).

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association between exposure to NDMA and several forms of cancer (i.e., gastric and lung), with some consistency of evidence for gastric cancer and for exposure–response for lung cancer, the latter in studies in which matching or control for confounders was most extensive. Although estimated intakes in these investigations were based on dietary recall, and although confounding factors such as alcohol were not accounted for, the data fulfil, at least in part, some of the traditional criteria for causality of an association between ingestion of NDMA and cancer.

With the exception of a very extensive recent study, the identified carcinogenesis bioassays for NDMA are considered limited by current standards (e.g., single dose levels, small group sizes, limited histopathological examination). The weight of evidence of the carcinogenicity of NDMA in mammalian species is consistent and convincing. Moreover, the pattern of tumour development is characteristic of that for a mode of action of carcinogenesis involving direct interaction with genetic material. In available studies, NDMA has induced tumours in all species examined (mice, rats, hamsters), at relatively low doses in some cases, irrespective of the route of exposure (oral, inhalation); tumours were induced in a wide range of tissues, including the liver, Leydig cells, lungs, kidney, and nasal cavity, in the absence of significant non-neoplastic effects, in the limited number of studies in which these were well examined. Where it was reported, time to first tumour was relatively short. The incidence of specific tumours has been increased following administration of even a single dose or repeated doses for short periods (i.e., 2–3 weeks); tumours have also been observed in the offspring of exposed pregnant rats and mice.

NDMA has been consistently mutagenic and clastogenic in human and rodent cells exposed *in vitro*. Clear evidence of genetic effects has also been observed in a number of tissues from animals exposed to this substance. Notably, genotoxic effects have been observed in tissues (i.e., liver, kidney, lung) where tumours commonly arise following experimental exposure to NDMA and in germ cells.

DNA adducts (in particular, O^6-methylguanine) formed by the methyldiazonium ion generated during metabolism likely play a critical role in NDMA carcinogenicity. Observed variations in carcinogenicity among species and strains correlate well with variations in activity of O^6-methylguanine DNA-methyltransferase. Putative pathways for the metabolism of NDMA are similar in rodents and humans, and indeed the formation of O^6-methylguanine has been detected in human tissues exposed to NDMA.

Therefore, owing to the considerable evidence of carcinogenicity of NDMA in laboratory species, evidence of direct interaction with DNA consistent with tumour formation, and the apparent lack of qualitative species-specific differences in the metabolism of this substance, NDMA is highly likely to be carcinogenic to humans.

11.1.1.2 Non-neoplastic effects

Information on adverse health effects other than cancer in humans associated with exposure to NDMA is limited. In case reports, liver failure, brain haemorrhage, and death have been attributed to the ingestion of NDMA. Effects resulting from exposure to unspecified amounts of airborne NDMA have included an enlarged liver and spleen, hepatic cirrhosis, jaundice, ascites, and death.

Data on non-neoplastic effects in laboratory animals associated with exposure to NDMA are also inadequate, attributable primarily to the focus on its carcinogenicity. Effects on the liver and kidney in repeated-dose toxicity studies (>0.2 mg NDMA/kg body weight per day), embryo toxicity and embryo lethality in single-dose developmental studies (20–30 mg/kg body weight), and a range of immunological effects (suppression of humoral- and cell-mediated immunity) reversible at lowest concentrations (5 mg NDMA/litre) have been reported.

11.1.2 Dose–response analyses

The principal route of human exposure to NDMA for the general population, including those exposed in the vicinity of point sources, is ingestion.[1] Moreover, information on exposure–response for the critical endpoint following inhalation and dermal exposure to NDMA is limited. Therefore, quantitation of dose–response is limited here to exposure via ingestion.

Scaling for variations in the ratios of surface area to body weight between rodent species and humans was not considered appropriate for the measures of exposure–response developed on the basis of experimental data in animals, since it is highly probable that the carcinogenicity of NDMA is mediated primarily through the generation of an active metabolite (i.e., the methyldiazonium ion).

[1] Estimated exposure would be higher if the population is assumed to be exposed continuously to the maximum concentration of NDMA in indoor air (see Table 2).

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11.1.2.1 Carcinogenicity

Cancer is clearly the critical end-point for quantitation of exposure–response for risk characterization of NDMA. This has been the best characterized end-point for this substance. Moreover, in general, tumours occur at lowest concentration, compared with those typically reported to induce non-cancer effects. An increased incidence of hepatic tumours was observed at doses as low as approximately 0.1 mg/kg body weight per day in rats (Brantom, 1983; Peto et al., 1991a,b), and the genotoxicity of NDMA (including formation of putatively critical adducts with DNA), for which the weight of evidence is exceedingly consistent and convincing, undoubtedly plays a critical role in tumour induction. A 2-fold increase in stillbirths and neonatal deaths (combined) was observed in mice receiving an estimated daily intake of 0.02 mg NDMA/kg body weight per day for 75 days prior to mating and throughout pregnancy and lactation. However, exposure to NDMA had no effect upon maternal fluid consumption, litter size, or average body weight of the weanlings, and there were no consistent gross or histopathological abnormalities in the stillborn fetuses or dead neonates to account for the increased mortality. Moreover, increased mortality was not observed in another study in which mice were administered higher doses of the nitrosamine (i.e., a single intraperitoneal injection of 7.4 mg NDMA/kg body weight on day 16 or 19 of gestation) (Anderson et al., 1989).

Quantitation of exposure–response for cancer for NDMA is based on studies in laboratory animals, since existing epidemiological data, although suggestive of a possible association between ingestion of NDMA and cancer, are inadequate to serve as a basis for characterization of exposure–response. There appear to be no *qualitative* differences in metabolism of NDMA between humans and laboratory animals, and there is no reason to believe that humans would respond qualitatively differently.

By far the most suitable study for exposure–response analyses of the carcinogenic effects of NDMA is that reported by Brantom (1983) and Peto et al. (1991a,b), which involved the administration of NDMA in drinking-water to a large number ($n = 15$) of large dose groups ($n = 60$) of male and female rats. Other available bioassays are considerably more limited — i.e., single dose groups, small group sizes, and histopathological examination often restricted to one tissue.

Quantitation of exposure–response for cancer involved calculation of the tumorigenic dose$_{05}$ (TD_{05}; i.e., the dose level that causes a 5% increase in tumour incidence over background).[1] The lowest TD_{05} was 34 µg/kg body weight per day for the development of biliary cystadenomas in female rats. This equates to a unit risk of 1.5×10^{-3} per µg/kg body weight (i.e., 0.05/34).

11.1.2.2 Non-neoplastic effects

Information on non-neoplastic effects in humans and experimental animals associated with exposure to NDMA is inadequate to characterize exposure–response.

Effects on the liver (i.e., hepatocyte vacuolization, portal venopathy, and necrosis/haemorrhage) and kidney (i.e., glomerulus dilatation and slight thickening of the Bowman's capsule), "congestion" in the spleen and lungs, and gastrointestinal haemorrhage have been reported in short- and medium-term studies of animals receiving greater than 0.2 mg NDMA/kg body weight per day. Embryo toxicity and embryo lethality have been observed in a number of inadequately reported studies of often non-standard protocol following oral exposure to high (maternally toxic) doses in the range of 20–30 mg/kg body weight per day or lower doses upon repeated exposure (1.4–2.9 mg/kg body weight per day by gavage or 5 mg/kg body weight per day in diet); teratogenicity has not been reported. In one report of a single-generation study (Anderson et al., 1978) in mice, the number of stillbirths and neonatal deaths (combined) was increased 2-fold at 0.1 mg/litre (estimated daily intake of 0.02 mg NDMA/kg body weight per day). However, confidence in the significance of this observation is mitigated by the lack of a more reliable estimate of intake, the absence of significant effects on other reproductive parameters, the lack of histopathological changes to account for the increased mortality, as well as the observation of no increased fetal mortality in dams administered a higher total dose of NDMA (Anderson et al., 1989).

Although suppression of cell- and humoral-mediated immune responses was reported in mice consuming doses greater than approximately 1 mg/kg body weight per day in drinking-water for 30–120 days, effects were fully reversible within 30 days of cessation of exposure.

Based on available documented studies, therefore, non-neoplastic effects of NDMA, where they have been observed, have typically occurred (except for one report of the single-generation reproduction study) at doses greater than those at which increases in tumour incidence have been reported in other studies (i.e., the

[1] Additional information on calculation of the TD_{05} is presented in Appendix 4.

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latter was observed at doses as low as about 0.1 mg/kg body weight per day in rats). In addition, in view of the likely critical role of the genotoxicity of NDMA in the induction of tumours, for which the weight of evidence is consistent and convincing, cancer is clearly the critical end-point for quantitation of exposure–response for risk characterization. Measures based on this end-point will be protective for other reported non-neoplastic effects.

11.1.3 Sample risk characterization

For substances such as NDMA, for which it is likely that the mode of action for the induction of tumours involves direct interaction with genetic material, quantitative estimates of carcinogenic potency (i.e., the TD_{05}) may be compared with estimates of exposure to characterize risk. In the sample country (Canada), with the exception of monitoring of NDMA in water supplies in Ontario, most of the sampling and analyses for this contaminant in the general environment have been source directed — i.e., confined to foodstuffs in which it is most likely to be present or media in the vicinity of industrial sources.[1] The margins between the lowest value for the TD_{05} (i.e., 34 µg/kg body weight per day) and the highest reasonable worst-case estimates for the intake of NDMA by individuals in Canada (see Table 2) — that is, for children (0.5–4 years) with intakes from air, water, and food (0.029 µg/kg body weight per day), for children (0.5–4 years) exposed to ETS-contaminated indoor air (0.13 µg/kg body weight per day), or for infants (0–0.5 years) consuming contaminated groundwater (0.31 µg/kg body weight per day) — are low (approximately 1170, 260, and 110, respectively), equating to low dose risks of $>10^{-5}$. Risks for ambient drinking-water are between 10^{-7} and 10^{-5}. It should be noted that the estimates of intake from food representative of the situation today are probably lower, due to the impact of subsequent introduction of changes in food processing and controls to limit the formation of NDMA. NDMA is a genotoxic carcinogen, and exposure should be reduced to the extent possible.

11.1.4 Uncertainties and degree of confidence in human health risk characterization

Non-neoplastic effects associated with exposure to NDMA have not been well studied. Although non-neoplastic effects in laboratory animals have typically been observed only at dose levels higher than those associated with increased tumour incidence (approximately 0.1 mg/kg body weight per day in rats), in one report, stillborn and neonatal deaths (combined) were observed in a single-generation study in mice receiving an estimated intake of approximately 0.02 mg/kg body weight per day for 75 days. While there is uncertainty surrounding the biological significance of this finding, further experimental work in this area would provide more definitive information concerning potential reproductive effects linked to long-term exposure to low levels of NDMA.

There is a high degree of certainty that the genotoxicity of NDMA (likely involving the formation of O^6-methylguanine in DNA) is critical in the mechanism of carcinogenicity of this substance. Also, due to the unusually large number of dose groups in the critical study, characterization of exposure–response for induction of tumours by NDMA in laboratory animals is considered to be optimal.

Comparison of the highest TD_{05} identified from the study in which exposure–response was best characterized (i.e., 82 µg/kg body weight per day for hepatic carcinomas in female rats) with the highest reasonable worst-case estimates for the intake of NDMA by individuals in Canada (in section 11.1.3) would yield margins approximately 2.4-fold (i.e., 82 µg/kg body weight per day ÷ 34 µg/kg body weight per day) higher than those derived (section 11.1.3) on the basis of the hepatic biliary cystadenomas in female rats.

11.2 Evaluation of environmental effects

11.2.1 Terrestrial assessment end-points

Since NDMA is not persistent in the environment, environmental effects are most likely to occur near point sources. Results of various industry and municipal surveys indicate that most releases of NDMA are to water. When NDMA is released to water, nearly all of it remains and reacts in the water phase. Based on the short half-life of NDMA in air and the amounts being released to air, it is unlikely that effects will occur on wildlife near point sources. Since there are no detectable releases to sediment and soil, and as NDMA does not move from water to these compartments, effects on wildlife do not appear to be of concern. Therefore, the assessment of NDMA released to water focuses on organisms exposed in water near point sources.

11.2.2 Aquatic assessment end-points

Assessment end-points include abundance and survival of fish, invertebrates, amphibians, and algae. These organisms are an integral part of ecosystems, as each trophic level provides food for higher levels in the aquatic food-chain. For example, algae are primary producers, forming the base of the food-chain. The abundance and productivity of phytoplankton are important to aquatic ecosystems, because phytoplankton provides

[1] NDMA was not detected in a single survey of ambient air not impacted by point sources.

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food for a variety of planktivorous organisms and thus controls energy flow in a portion of the ecosystem. Cladocerans such as *Daphnia magna* consume bacteria and phytoplankton and are themselves consumed by many fish species. Various fish species feed on aquatic vegetation, phytoplankton, zooplankton, benthic invertebrates, benthic vertebrates, etc. Vertebrate omnivores provide food for vertebrate carnivores. The most sensitive measurement end-point identified for aquatic species was growth of the green alga (*Selenastrum capricornutum*).

As NDMA is a potent inducer of acute toxic and chronic neoplastic lesions in aquatic species, assessment end-points reflecting these effects are mentioned here. In nearly all of the studies conducted on a variety of species at different trophic levels, tumours have resulted from exposure to NDMA. Although a tumorigenic end-point is not traditionally used as an indicator of a population-level effect, it may have implications if an endangered species is found in the area of discharge of effluent containing NDMA. At this time, however, implications of tumour induction in environmental species are unclear.

11.2.3 Sample environmental risk characterization

11.2.3.1 Aquatic organisms

Based on the sources and fate of NDMA, and because data on concentrations in ambient water near point sources are not available, end-of-pipe concentrations in final effluent were used as a measure of exposure of aquatic organisms. Recent concentrations have been selected to reflect present exposures. The highest concentration of NDMA in wastewater discharged to a water body was 0.266 µg/litre. Although this concentration is expected to decrease, as the company installed a wastewater treatment plant in1998, this value is used as the estimated exposure value (EEV) in the hyperconservative analysis of long-term exposure for aquatic plants and animals.

For long-term exposure of aquatic organisms to NDMA, the critical toxicity value (CTV) is 4000 µg/litre, based on a 13-day EC_{50} for inhibition of growth in the green alga (*Selenastrum capricornutum*). This value was selected from a data set composed of several studies conducted on at least eight species of aquatic organisms, which include phytoplankton, zooplankton, fish, amphibians, and invertebrates. It is important to note that in the second most sensitive study, tumours were present in the organism. Khudoley (1977) reported that liver tumours were induced in 44% of frogs (*Rana temporaria*) after 203 days of exposure at a concentration of 5000 µg/litre. Again, as was indicated in section 11.2.2 , the implications of tumour induction as a population-level effect cannot be determined at this time.

For a hyperconservative analysis, the estimated no-effects value (ENEV) is derived by dividing the CTV by an application factor of 100. This accounts for the uncertainty surrounding the conversion of a short-term EC_{50} to a chronic no-effects value, the extrapolation from laboratory to field conditions, and interspecies and intraspecies variations in sensitivity. As a result, the ENEV is 40 µg/litre.

The hyperconservative quotient is calculated by dividing the EEV of 0.266 µg/litre by the ENEV for green algae as follows:

$$\text{Quotient} = \frac{\text{EEV}}{\text{ENEV}}$$

$$= \frac{0.266\ \mu g/\text{litre}}{40\ \mu g/\text{litre}}$$

$$= 0.007$$

Since the hyperconservative quotient is less than one, it is unlikely that NDMA releases will cause adverse effects on populations of aquatic organisms in the sample country.

11.2.4 Discussion of uncertainty

Regarding effects of NDMA on aquatic organisms, there is uncertainty in the extrapolation from available toxicity data to potential ecosystem effects. The toxicity data set for aquatic biota, however, is considered adequate, as it includes a variety of species from different trophic levels. While some of the studies are relatively old (1960s–1980s), they are generally of good quality and are considered acceptable for the assessment.

12. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

NDMA has been classified by the International Agency for Research on Cancer (IARC, 1987) as a "probable human carcinogen (Group 2A)," based upon sufficient evidence of a carcinogenic effect in experimental animal species and the demonstrated similarities in its metabolism by human and rodent tissues.

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APPENDIX 1 — SOURCE DOCUMENT

Environment Canada & Health Canada (2001)

Copies of the *Canadian Environmental Protection Act* Priority Substances List assessment report (Environment Canada & Health Canada, 2001) and unpublished supporting documentation for NDMA may be obtained from:

Commercial Chemicals Evaluation Branch
Environment Canada
14th floor, Place Vincent Massey
351 St. Joseph Blvd.
Hull, Quebec
Canada K1A 0H3

or

Environmental Health Centre
Health Canada
Address Locator: 0801A
Tunney's Pasture
Ottawa, Ontario
Canada K1A 0L2

Initial drafts of the supporting documentation and assessment report for NDMA were prepared by staff of Health Canada and Environment Canada. H. Hirtle contributed additional information in the preparation of the draft CICAD.

Environmental sections of the assessment report were reviewed externally by J. Ballantine (Health Canada), A. McLarty (Ontario Ministry of the Environment), E. McBean and J. Kochany (*Conestoga-Rovers & Associates*), and D. Carlisle (Brez-Carlisle Inc.).

In order to address primarily adequacy of coverage, sections of the supporting documentation pertaining to human health were reviewed externally by B. Birmingham (Ontario Ministry of the Environment) and R. Brecher (Globaltox International Consultants, Inc.).

Accuracy of reporting, adequacy of coverage, and defensibility of conclusions with respect to hazard characterization and dose–response analysis were considered at a panel meeting of the following members, convened by *Toxicology Excellence for* Risk Assessment (TERA) on 12 August 1999 in Ottawa, Ontario:

M. Bogdanffy, DuPont Haskel Laboratory
J. Christopher, California Environmental Protection Agency
M. Dourson, TERA
S. Felter, Procter & Gamble
J. Mandel, Exponent
R. Rudel, Silent Spring Institute
V. Walker, New York State Department of Health

APPENDIX 2 — CICAD PEER REVIEW

The draft CICAD on NDMA was sent for review to institutions and organizations identified by IPCS after contact with IPCS national contact points and Participating Institutions, as well as to identified experts. Comments were received from:

A. Aitio, *International* Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

M. Baril, International Programme on Chemical Safety/ Institut de Recherche en Santé et en Sécurité du Travail du Québec, Montreal, Quebec, Canada

R. Benson, *Drinking* Water Program, US Environmental Protection Agency, Denver, CO, USA

R. Cary, Health and Safety Executive, Bootle, Merseyside, United Kingdom

R. Chhabra, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC, USA

C. Elliott-Minty, Health and Safety Executive, Bootle, Merseyside, United Kingdom

E. Frantik, National Institute of Public Health, Center of Industrial Hygiene and Occupational Diseases, Praha, Czech Republic

R. Hertel, Federal Institute for Health Protection of Consumers and Veterinary Medicine, Berlin, Germany

T.G. Hrnsi, National Institute of Public Health, Oslo, Norway

A.P. Hugenholtz, Bureau of Chemical Safety, Health *Canada, Ottawa, Ontario, Canada*

E. Srderlund, National Institute of Public Health, Oslo, Norway

U. Steinus, Karolinska Institute, Stockholm, Sweden

Y.-W. Stevens, Agency for Toxic Substances and Disease Registry, Atlanta, GA, USA

K. Ziegler-Skylakakis, Commission of the European Communities/European Union, Luxembourg

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APPENDIX 3 — CICAD FINAL REVIEW BOARD

Geneva, Switzerland, 8–12 January 2001

Members

Dr A.E. Ahmed, Molecular Toxicology Laboratory, Department of Pathology, University of Texas Medical Branch, Galveston, TX, USA

Mr R. Cary, Health and Safety Executive, Merseyside, United Kingdom (*Chairperson*)

Dr R.S. Chhabra, General Toxicology Group, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC, USA

Dr S. Czerczak, Department of Scientific Information, Nofer Institute of Occupational Medicine, Lodz, Poland

Dr S. Dobson, Centre for Ecology and Hydrology, Cambridgeshire, United Kingdom

Dr O.M. Faroon, Division of Toxicology, Agency for Toxic Substances and Disease Registry, Atlanta, GA, USA

Dr H. Gibb, National Center for Environmental Assessment, US Environmental Protection Agency, Washington, DC, USA

Dr R.F. Hertel, Federal Institute for Health Protection of Consumers and Veterinary Medicine, Berlin, Germany

Dr A. Hirose, Division of Risk Assessment, National Institute of Health Sciences, Tokyo, Japan

Dr P.D. Howe, Centre for Ecology and Hydrology, Cambridgeshire, United Kingdom (*Rapporteur*)

Dr D. Lison, Industrial Toxicology and Occupational Medicine Unit, Université Catholique de Louvain, Brussels, Belgium

Dr R. Liteplo, Existing Substances Division, Bureau of Chemical Hazards, Health Canada, Ottawa, Ontario, Canada

Dr I. Mangelsdorf, Chemical Risk Assessment, Fraunhofer Institute for Toxicology and Aerosol Research, Hanover, Germany

Ms M.E. Meek, Existing Substances Division, Safe Environments Program, Health Canada, Ottawa, Ontario, Canada (*Vice-Chairperson*)

Dr S. Osterman-Golkar, Department of Molecular Genome Research, Stockholm University, Stockholm, Sweden

Dr J. Sekizawa, Division of Chem-Bio Informatics, National Institute of Health Sciences, Tokyo, Japan

Dr S. Soliman, Department of Pesticide Chemistry, Faculty of Agriculture, Alexandria University, El-Shatby, Alexandria, Egypt

Dr M. Sweeney, Education and Information Division, National Institute for Occupational Safety and Health, Cincinnati, OH, USA

Professor M. van den Berg, Environmental Sciences and Toxicology, Institute for Risk Assessment Sciences, University of Utrecht, Utrecht, The Netherlands

Observers

Dr W.F. ten Berge, DSM Corporate Safety and Environment, Heerlen, The Netherlands

Dr K. *Ziegler-Skylakakis, Commission of the European* Communities, Luxembourg

Secretariat

Dr A. Aitio, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Dr Y. Hayashi, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Dr P.G. Jenkins, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Dr M. Younes, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

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APPENDIX 4 — CALCULATION OF TUMORIGENIC DOSE$_{05}$

The tumorigenic dose$_{05}$ (TD$_{05}$; i.e., the dose level that causes a 5% increase in tumour incidence over background) was calculated by first fitting the multistage model to the dose–response data. The multistage model is given by

$$P(d) = 1 - e^{-q_0 - q_1 d - \ldots - q_k d^k}$$

where d is dose, k is the number of dose groups in the study minus one, $P(d)$ is the probability of the animal developing a tumour at dose d, and $q_i > 0$, $i = 1,\ldots, k$ are parameters to be estimated. TD$_{05}$s were then calculated as the dose D that satisfies

$$\frac{P(D) - P(0)}{1 - P(0)} = 0.05$$

A chi-square lack of fit test was performed for each of the three tumour types. The degrees of freedom for this test are equal to k minus the number of q_i's for which estimates are non-zero. A *P*-value less than 0.05 indicates a significant lack of fit.

The study reported by Brantom (1983) and Peto et al. (1991a,b) contained 15 dose groups and controls, which is unusually large. Upper dose groups for which there was downturn in the dose–response curve were first eliminated from calculations of the TD$_{05}$. These dose groups add no information to the shape of the dose–response curve in the range of the TD$_{05}$ and contribute to lack of fit of the model. In addition, extreme downturn is likely a sign that animals are dying of some other cause before having a chance to develop the tumour of interest.

Two methods were used to fit models to the large number of dose groups. In the first method, quadratic models (i.e., models with $k = 2$) were fit to the full set of data, less any dose groups contributing to downturn at the upper end of the dose–response curve. Any model with k larger than 2 did not converge when fitting models to the full data set. The second method involved reducing the number of dose groups to 10 (or less) by first eliminating upper dose groups with downturn and then collapsing adjacent similar dose groups together. Collapsing was accomplished by averaging the dose level and totalling the number of tumours for the two groups. Global82 (Howe & Crump, 1982) was then used to fit full multistage models to the reduced data. With the exception of biliary cystadenomas in females, these models did not show significant lack of fit. However, they generally appeared to overestimate the risk in the range of the TD$_{05}$, resulting in TD$_{05}$ values that might be overly conservative. There was no evidence of a dose–response relationship for haemangiosarcomas in females; these data were not modelled, therefore, for the purpose of calculating a TD$_{05}$.

After reducing the data to 10 dose groups, the multistage model still occasionally exhibited lack of fit, due in large part to a levelling off of the dose–response relationship at higher doses. Since a good fit in the range of the TD$_{05}$ is required, upper dose groups were systematically eliminated until a reasonable fit was achieved. The data finally used to compute TD$_{05}$s for hepatic tumours in the male and female rats from the Brantom (1983) and Peto et al. (1991a,b) study are presented in Tables A-1 and A-2.

After comparing the two methods of model fitting, the second was judged to provide a better description of the dose–response relationship in the range of the TD$_{05}$. These fits were used to generate the final TD$_{05}$s. The TD$_{05}$s and model-fitting information are presented in Table A-3 and Figure A-1.

Table A-1: Data on hepatic carcinogenicity in male rats used for modelling.

Carcinoma		Haemangiosarcoma		Biliary cystadenoma	
Intake (mg/kg body weight per day)	Incidence	Intake (mg/kg body weight per day)	Incidence	Intake (mg/kg body weight per day)	Incidence
0	2/192	0	2/192	0	2/192
0.0020	2/96	0.002	0/96	0.0020	4/96
0.0080	3/96	0.005	1/48	0.0080	4/96
0.0330	4/96	0.011	2/48	0.0330	2/96
0.0760	11/96	0.022	0/48	0.0760	10/96
0.1200	26/96	0.044	1/48	0.1200	24/96
0.1960	44/96	0.065	1/48	0.1960	26/96
0.3045	66/96	0.087	6/48	0.3045	33/96
		0.109	6/48		
		0.131	14/48		

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Table A-2: Data on hepatic carcinogenicity in female rats used for modelling.

Carcinoma		Biliary cystadenoma	
Intake (mg/kg body weight per day)	Incidence	Intake (mg/kg body weight per day)	Incidence
0	2/192	0	4/192
0.0035	0/96	0.002	1/48
0.0145	4/96	0.005	4/48
0.057	8/96	0.010	0/48
0.134	10/96	0.019	3/48
0.210	10/96	0.038	5/48
0.344	19/96	0.076	7/48
0.459	18/48	0.115	34/48
0.612	33/48		

Table A-3: TD_{05}s for NDMA.

	TD_{05} (µg/kg body weight per day)	95% lower confidence limit on TD_{05}	Chi-square	df	*P*-value
Male rats					
Hepatic carcinoma	38	24	2.17	5	0.82
Hepatic haemangiosarcoma	78	48	7.67	6	0.26
Hepatic biliary cystadenoma	35	29	10.25	6	0.11
Female rats					
Hepatic carcinoma	82	61	7.36	5	0.19
Hepatic biliary cystadenoma	34	18	7.036	5	0.22

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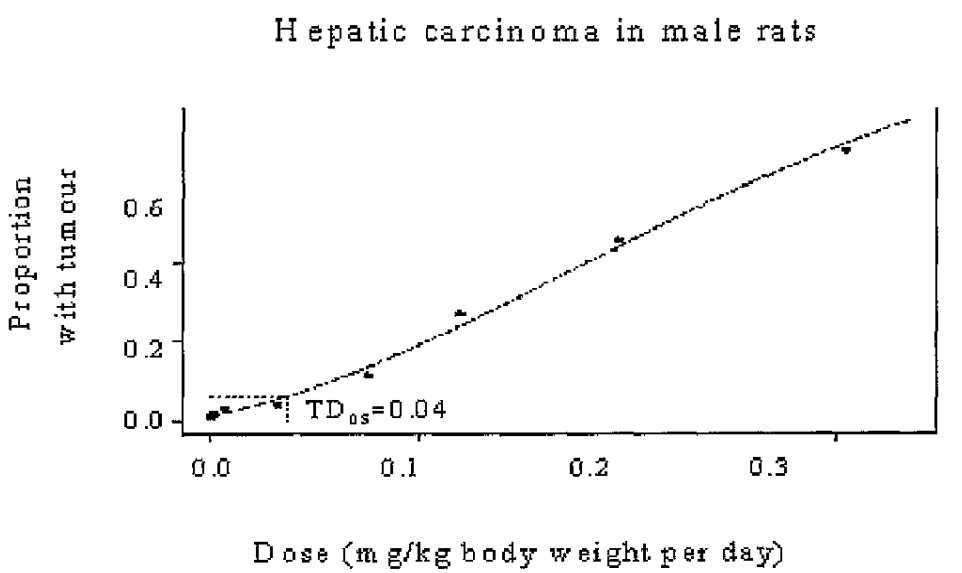

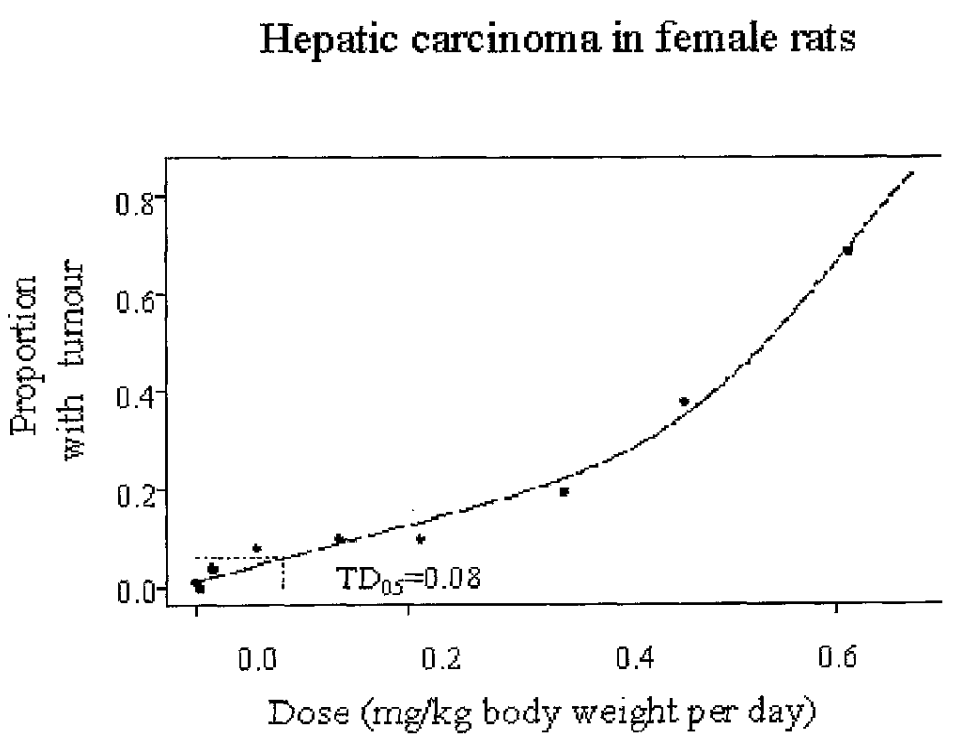

Figure A-1: TD_{05}s for NDMA.

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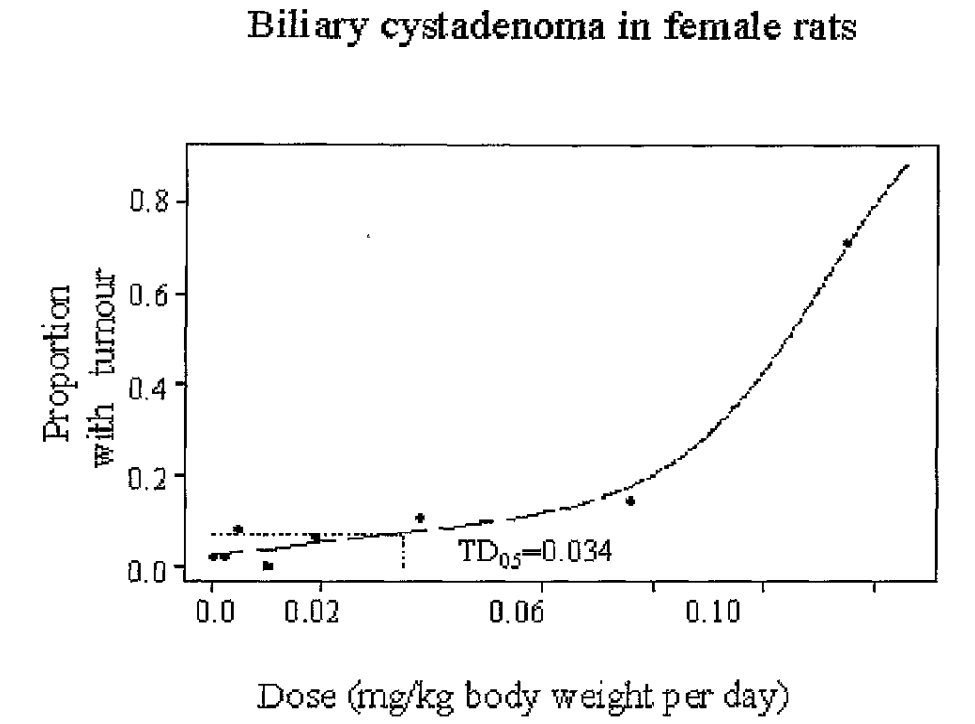

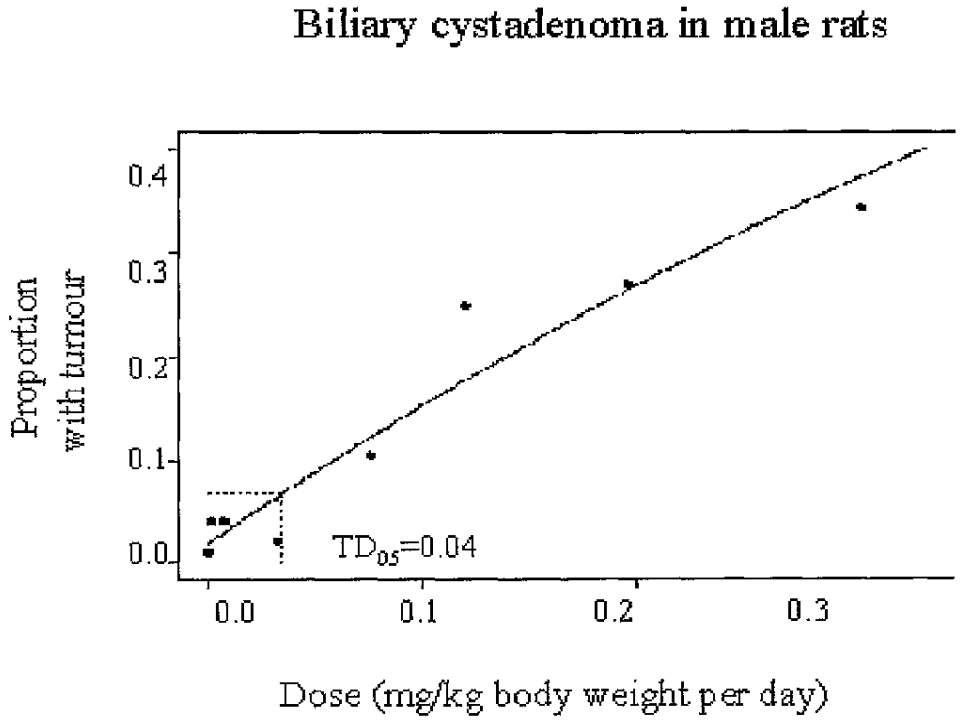

Figure A-1: TD_{05}s for NDMA.

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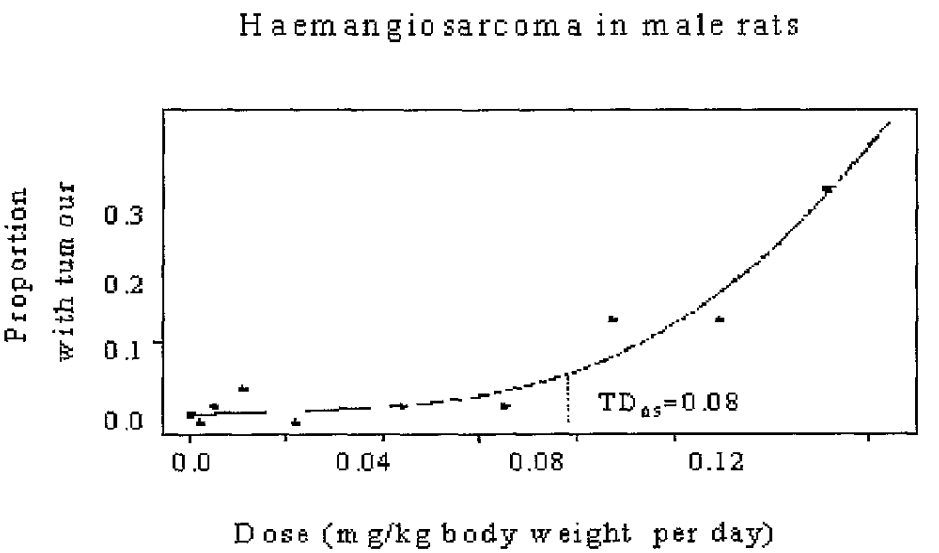

Figure A-1: TD_{05}s for NDMA.

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N-NITROSODIMETHYLAMINE

0525
March 2001

CAS No: 62-75-9
RTECS No: IQ0525000
UN No: 2810
EC No: 612-077-00-3

Dimethylnitrosamine
N-Methyl-N-nitrosomethylamine
DMN
$C_2H_6N_2O$ / $(CH_3)_2NN=O$
Molecular mass: 74.1

TYPES OF HAZARD/ EXPOSURE	**ACUTE HAZARDS/SYMPTOMS**	**PREVENTION**	**FIRST AID/FIRE FIGHTING**
FIRE	Combustible.	NO open flames.	Powder, carbon dioxide.
EXPLOSION			

EXPOSURE		**AVOID ALL CONTACT!**	**IN ALL CASES CONSULT A DOCTOR!**
Inhalation	Sore throat. Cough. Nausea. Diarrhoea. Vomiting. Headache. Weakness.	Ventilation, local exhaust, or breathing protection.	Fresh air, rest. Refer for medical attention.
Skin	Redness. Pain.	Protective gloves.	Remove contaminated clothes. Rinse skin with plenty of water or shower.
Eyes	Pain. Redness.	Face shield, or eye protection in combination with breathing protection.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion	Abdominal cramps. (Further see Inhalation).	Do not eat, drink, or smoke during work. Wash hands before eating.	Give a slurry of activated charcoal in water to drink. Induce vomiting (ONLY IN CONSCIOUS PERSONS!). Refer for medical attention.

SPILLAGE DISPOSAL	**PACKAGING & LABELLING**	
Evacuate danger area! Collect leaking and spilled liquid in sealable containers as far as possible. Absorb remaining liquid in sand or inert absorbent and remove to safe place. Chemical protection suit including self-contained breathing apparatus.	T+ Symbol N Symbol R: 45-25-26-48/25-51/53 S: 53-45-61 Note: E UN Hazard Class: 6.1 UN Pack Group: I	Do not transport with food and feedstuffs. Unbreakable packaging; put breakable packaging into closed unbreakable container.

EMERGENCY RESPONSE	**STORAGE**
Transport Emergency Card: TEC (R)-61G61b	Separated from strong oxidants, food and feedstuffs. Cool. Keep in the dark. Well closed.

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International Programme on Chemical Safety

UNEP

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0525	N-NITROSODIMETHYLAMINE

IMPORTANT DATA

Physical State; Appearance
YELLOW OILY LIQUID

Chemical dangers
The substance decomposes on heating producing nitrogen oxides. Reacts with strong oxidants and strong bases.

Occupational exposure limits
TLV: A3, skin (ACGIH 2000).
MAK: Class 2 (2000)

Routes of exposure
The substance can be absorbed into the body by inhalation and by ingestion.

Inhalation risk
No indication can be given about the rate in which a harmful concentration in the air is reached on evaporation of this substance at 20°C.

Effects of short-term exposure
The substance is irritating to the eyes, the skin and the respiratory tract. The substance may cause effects on the liver, resulting in jaundice. The effects may be delayed. See Notes. Medical observation is indicated.

Effects of long-term or repeated exposure
The substance may have effects on the liver, resulting in liver function impairment and cirrhosis. This substance is probably carcinogenic to humans.

PHYSICAL PROPERTIES

Boiling point: 151°C
Relative density (water = 1): 1.0
Solubility in water: very good
Vapour pressure, Pa at 20°C: 360
Relative vapour density (air = 1): 2.56
Flash point: 61°C
Octanol/water partition coefficient as log Pow: -0.57

ENVIRONMENTAL DATA

NOTES

The symptoms of jaundice do not become manifest until some hours have passed. Environmental effects from the substance have not been investigated adequately.

ADDITIONAL INFORMATION

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RÉSUMÉ D'ORIENTATION

Ce CICAD relatif à la *N*-nitrosodiméthylamine (NDMA) a été préparé conjointement par la Direction de l'Hygiène du Milieu de Santé Canada et la Direction de l'Evaluation des produits chimiques commerciaux d'Environnement Canada à partir d'une documentation rédigée simultanément dans le cadre du programme sur les substances prioritaires prévu par la *Loi canadienne sur la protection de l'environnement* (LCPE). Les études sur les substances prioritaires prescrites par la LCPE ont pour objectif d'évaluer les effets potentiels sur la santé humaine d'une exposition indirecte à celles de ces substances qui sont présentes dans l'environnement ainsi que leurs effets sur l'environnement lui-même. Bien que l'exposition professionnelle n'ait pas été le sujet du document initial (Environnement Canada & Santé Canada, 2001), des données sur la question été incluses dans le présent CICAD. La présente mise au point prend en compte les données publiées jusqu'en août 1999 en ce qui concerne les effets sanitaires et jusqu'à fin fin août 1998 en ce qui concerne les effets sur l'environnement.[1] D'autres mises au point ont été également consultées, à savoir celles du CIRC (1978), de l'OME (1991, 1998) et de BIBRA Toxicology International (1997, 1998). Des renseignements sur la nature de l'examen par des pairs et la disponibilité du document de base sont donnés à l'appendice 1. Les informations concernant l'examen par des pairs du présent CICAD figurent à l'appendice 2. Ce CICAD a été approuvé en tant qu'évaluation internationale lors d'une réunion du Comité d'évaluation finale qui s'est tenue à Genève (Suisse), du 8 au 12 janvier 2001. La liste des participants à cette réunion se trouve à l'appendice 3. La fiche internationale sur la sécurité chimique de la NDMA (ICSC 0525), préparée par le Programme international sur la sécurité chimique (IPCS, 1993), est également reproduite dans le présent document.

La *N*-nitrosodiméthylamine (NDMA) est la plus simple des dialkylnitrosamines. Bien que n'étant plus utilisée dans l'industrie ou le commerce ni au Canada, ni aux Etats-Unis, elle continue néanmoins d'être libérée dans l'environnement comme sous-produit ou contaminant par diverses installations industrielles et par les stations municipales de traitement des eaux usées. Ce sont les usines de pesticides, de pneumatiques, de colorants et les unités de production d'alkylamines qui en rejettent le plus. De la NDMA peut également se former dans les conditions naturelles dans l'air, l'eau et le sol par suite de certains processus chimiques, photochimiques ou biologiques et on en a mis en évidence dans l'eau de boisson et dans les gaz d'échappement des automobiles.

C'est principalement par photolyse que la NDMA s'élimine des eaux de surface, de l'atmosphère et du sol. Toutefois, dans les eaux superficielles riches en substances organiques et matières en suspension, la photodécomposition est très ralentie. Dans les eaux des nappes phréatiques et dans le sol, c'est la biodégradation qui constitue la voie d'élimination prédominante. La NDMA a vraisemblablement peu de chances d'être transportée sur de longues distances ou de se répartir dans le sol et les sédiments. En raison de sa solubilité et de la faible valeur de son coefficient de partage, la NDMA a la possibilité de passer par lessivage dans les eaux souterraines et de s'y maintenir. Elle subit une métabolisation et ne s'accumule pas. Elle n'est pas présente en quantités décelables dans les eaux de surface, sauf en cas de contamination localisée aux alentours de sites industriels, où l'on a pu mesurer des concentrations allant jusqu'à 0,266 µg par litre au débouché de certains émissaires.

Selon des enquêtes limitées effectuées dans le pays sur lequel on s'est basé pour caractériser le risque type (le Canada), la NDMA n'est pas décelable dans l'air ambiant, sauf à proximité de sites industriels. En revanche, de faibles concentrations de NDMA - provenant de stations de traitement ou d'eaux souterraines contaminées par des effluents industriels - ont été mesurées dans de l'eau de consommation. On a également mis en évidence la présence de NDMA dans diverses denrées alimentaires, le plus souvent dans de la bière, des salaisons ou des fumaisons, des produits pisciaires et dans certains fromages avec, il est vrai, une diminution de la concentration ces dernières années en raison d'un changement dans le mode de traitement de ces produits. Le consommateur peut également être exposé à la NDMA contenue dans d'autres produits tels que les cosmétiques et les produits de soins, les objets en caoutchouc et le tabac.

La NDMA est indubitablement cancérogène, comme le montrent les recherches en laboratoire selon lesquelles ce composé provoque l'apparition de tumeurs à dose relativement faible chez toutes les espèces étudiées. On a en outre la preuve indiscutable du

[1] Les nouvelles données notées par les auteurs et obtenues par un dépouillement de la littérature effectué avant la réunion du Comité d'évaluation finale ont été examinées compte tenu de leur influence probable sur les conclusions essentielles de la présente évaluation, le but étant avant tout d'établir si leur prise en compte serait prioritaire lors d'une prochaine mise à jour. Les auteurs ayant estimé qu'elles apportaient des éléments d'information supplémentaires, on a ajouté des données plus récentes encore que non essentielles pour la caractérisation des dangers ou l'analyse des relations dose-réponse.

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pouvoir mutagène et clastogène de la NDMA. Le mécanisme de la cancérisation induite par ce composé n'est pas encore totalement élucidé, mais on sait qu'au cours de sa métabolisation, il donne naissance à un ion méthyldiazonium dont les adduits avec l'ADN (notamment l'O^6-méthylguanine) jouent sans doute un rôle déterminant. Qualitativement, le métabolisme de la NDMA est analogue chez l'Homme et l'animal; on estime par conséquent que ce composé est très probablement également cancérogène pour l'Homme, sans doute à concentration relativement faible.

Comme on s'est surtout intéressé au pouvoir cancérogène de la NDMA, on ne dispose que de résultats de laboratoire limités concernant ses effets non néoplasiques. L'administration de doses répétées provoque des effets sur le foie et le rein et des études sur le développement consistant à administrer une dose unique ont mis en évidence une toxicité pour l'embryon pouvant aller jusqu'à la mort. Par ailleurs, on a fait état de divers effets immunologiques (dépression de l'immunité humorale et de l'immunité à médiation cellulaire) qui sont réversibles à faible concentration.

Il est clair que, s'agissant de la quantification de la relation dose-réponse en vue de la caractérisation du risque, c'est le cancer qui constitue le point d'aboutissement essentiel de l'action toxique de la NDMA. Outre que ce sont les effets les mieux caractérisés, en règle générale, ces tumeurs apparaissent à des concentrations beaucoup plus faibles que celles auxquelles des effets non néoplasiques sont habituellement observés. La dose tumorigène la plus faible ($CT_{0,5}$) pour l'apparition de tumeurs hépatiques (cystadénomes biliaires chez des rats femelles après exposition d'animaux des deux sexes) déterminée lors de l'étude qui a fourni les données essentielles sur ce point, a été de 34 µg/kg de poids corporel par jour. Cette valeur correspond à un risque unitaire de $1,5 \times 10^{-3}$ par µg de substance et par kg de poids corporel. En se basant sur l'estimation de la dose de NDMA absorbée avec l'air ambiant et une eau de boisson contaminée (eau souterraine) lors de la caractérisation du risque type, le risque au voisinage de sources industrielles ponctuelles de NDMA est évalué à $>10^{-5}$. En qui concerne le risque inhérent à la consommation d'eau de boisson contaminée, la valeur se situe entre 10^{-7} et 10^{-5}. La NDMA est un cancérogène génotoxique et l'exposition à ce composé doit être la plus faible possible.

On possède des données sur la toxicité aiguë et chronique du composé pour les organismes aquatiques. L'effet toxique constaté à la concentration la plus faible (4000 µg/litre) a consisté en une réduction de la croissance chez des algues. Cette caractérisation du risque type tient compte du fait que dans le pays retenu, la concentration en NDMA dans les eaux de surface est inférieure au seuil estimatif d'apparition d'effets nocifs chez les organismes aquatiques. On n'a pas trouvé de données concernant la présence de NDMA dans les sédiments ou le sol du pays témoin.

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RESUMEN DE ORIENTACIÓN

Este CICAD sobre la *N*-nitrosodimetilamina (NDMA), preparado conjuntamente por la Dirección de Higiene del Medio del Ministerio de Salud del Canadá y la División de Evaluación de Productos Químicos Comerciales del Ministerio de Medio Ambiente del Canadá, se basa en la documentación preparada al mismo tiempo como parte del Programa de Sustancias Prioritarias en el marco de la *Ley Canadiense de Protección del Medio Ambiente* (CEPA). Las evaluaciones de sustancias prioritarias previstas en la CEPA tienen por objeto valorar los efectos potenciales para la salud humana de la exposición indirecta en el medio ambiente general, así como los efectos ecológicos. Aunque en el documento original no se abordó la exposición ocupacional (Ministerios de Medio Ambiente y de Salud del Canadá, 2001), en el presente CICAD se ha incluido información sobre este aspecto. En este examen se analizaron los datos identificados hasta el final de agosto de 1998 (efectos medioambientales) y agosto de 1999[1] (efectos en la salud humana). También se consultaron otros exámenes, entre ellos los del CIIC (1978), ATSDR (1989), OME (1991, 1998) y BIBRA Toxicology International (1997, 1998). La información relativa al carácter del examen colegiado y la disponibilidad del documento original figuran en el apéndice 1. La información sobre el examen colegiado de este CICAD aparece en el apéndice 2. Este CICAD se aprobó como evaluación internacional en una reunión de la Junta de Evaluación Final celebrada en Ginebra (Suiza) del 8 al 12 de enero de 2001. La lista de participantes en esta reunión figura en el apéndice 3. La Ficha internacional de seguridad química (ICSC 0525) para la NDMA, preparada por el Programa Internacional de Seguridad de las Sustancias Químicas (IPCS, 1993), también se reproduce en este documento.

La *N*-nitrosodimetilamina (NDMA) es la dialquilnitrosamina más sencilla. Aunque ya no se utiliza con fines industriales o comerciales en el Canadá o los Estados Unidos de América, se sigue liberando como subproducto y contaminante a partir de diversas industrias y de instalaciones de depuración de aguas residuales municipales. Las emisiones más importantes de NDMA proceden de la fabricación de plaguicidas, neumáticos de caucho, alquilaminas y colorantes. La NDMA se puede formar también en condiciones naturales en el aire, el agua y el suelo como resultado de procesos químicos, fotoquímicos y biológicos, y se ha detectado en el agua de bebida y en los gases de escape de los automóviles.

La fotolisis es la vía principal de eliminación de la NDMA de las aguas superficiales, el aire y el suelo. Sin embargo, en las aguas superficiales con concentraciones elevadas de sustancias orgánicas y materia en suspensión, la fotodegradación es mucho más lenta. En las aguas no superficiales y en el suelo, la biodegradación es la vía de eliminación más importante. Es poco probable que la NDMA recorra largas distancias suspendida en el aire o que se distribuya en el suelo y los sedimentos. Debido a su solubilidad y a su bajo coeficiente de reparto, la NDMA puede filtrarse a las aguas freáticas y persistir en ellas. Se metaboliza y no se bioacumula. En general, la NDMA no es detectable en las aguas superficiales, excepto en la contaminación localizada de zonas industriales, en las que se han medido concentraciones de efluentes de la etapa final de producción de hasta 0,266 µg/l.

En estudios limitados en el país en el cual se basa la caracterización del riesgo de muestra (es decir, el Canadá), no se ha detectado NDMA en el aire, salvo en las inmediaciones de zonas industriales. Se han detectado concentraciones bajas de NDMA en el agua de bebida, por ejemplo en instalaciones de tratamiento del agua o a partir de aguas freáticas contaminadas por efluentes industriales. Se ha demostrado la presencia de NDMA en algunos alimentos, en particular la cerveza, la carne curada, los productos pesqueros y algunos quesos, aunque en los últimos años las concentraciones de NDMA en estos productos han disminuido debido a cambios en la elaboración de los alimentos. También se puede sufrir exposición a la NDMA por el uso de productos de consumo que la contienen, por ejemplo cosméticos y productos de cuidado personal, productos que contienen caucho y productos de tabaco.

Sobre la base de los estudios de laboratorio en los cuales se han inducido tumores en todas las especies examinadas a dosis relativamente bajas, la NDMA es claramente carcinogénica. Hay pruebas abundantes de que la NDMA es mutagénica y clastogénica. Aunque no se conoce completamente su mecanismo de inducción de tumores, los aductos de ADN (en particular la O^6-metilguanina) formados por el ión metildiazonio generado durante el metabolismo tienen probablemente un papel decisivo. Desde el punto de vista cualitativo, el metabolismo de la NDMA parece ser semejante en las personas

[1] Se ha incluido nueva información destacada por los examinadores y obtenida en una búsqueda bibliográfica realizada antes de la reunión de la Junta de Evaluación Final para señalar sus probables repercusiones en las conclusiones esenciales de esta evaluación, principalmente con objeto de establecer la prioridad para su examen en una actualización. Se ha añadido información más reciente, no esencial para la caracterización del peligro o el análisis de la exposición-respuesta, que a juicio de los examinadores aumentaba el valor informativo.

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y los animales; en consecuencia, se considera muy probable que sea carcinogénica para las personas, incluso a niveles de exposición relativamente bajos.

Los datos sobre los efectos no neoplásicos en animales de laboratorio asociados con la exposición a la NDMA son limitados y pueden atribuirse principalmente a la atención que se presta a su carcinogenicidad. Se han notificado efectos en el hígado y el riñón en estudios de toxicidad de dosis repetidas, toxicidad y letalidad embrionarias en estudios de desarrollo de dosis única y una serie de efectos inmunológicos (supresión de la inmunidad humoral y mediada por células) reversibles con las concentraciones más bajas.

El cáncer es sin duda el efecto final crítico para la cuantificación de la exposición-respuesta en la caracterización del riesgo de la NDMA. Además de ser el mejor caracterizado, en general, los tumores se producen con la concentración más baja, en comparación con las notificadas normalmente como inductoras de efectos distintos del cáncer. La dosis tumorigénica$_{0,5}$ más baja para la inducción de tumores hepáticos en ratas macho y hembra expuestas a la NDMA en el estudio crítico fue de 34 µg/kg de peso corporal al día para la formación de cistadenomas biliares en hembras. Esto equivale a un riesgo unitario de $1,5 \times 10^{-3}$ por µg/kg de peso corporal. Basándose en la ingesta estimada de NDMA en el aire y en el agua de bebida contaminada (agua freática) en la caracterización del riesgo de muestra, los riesgos en las inmediaciones de fuentes puntuales industriales son $>10^{-3}$. Los relativos al agua de bebida son de 10^{-7} a 10^{-5}. La NDMA es un carcinógeno genotóxico y la exposición se debe reducir en la medida de lo posible.

Hay datos disponibles de toxicidad aguda y crónica para los organismos acuáticos. El efecto tóxico que se produjo con la concentración más baja fue una reducción del crecimiento de las algas con 4000 µg/l. En la caracterización del riesgo de muestra, las concentraciones de NDMA en las aguas superficiales del país en el que se ha realizado es inferior al umbral para los efectos adversos estimados en los organismos acuáticos. No se encontraron datos sobre las concentraciones de la NDMA en los sedimentos o en el suelo del país de muestra.

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